



# The New England Journal of Medicine

Formerly The Boston Medical and Surgical Journal

Established 1828

Published by the Massachusetts Medical Society under the Jurisdiction of  
The Committee on Publication

JANUARY-JUNE, 1942

8 Fenway, Boston



# MASSACHUSETTS MEDICAL SOCIETY

## OFFICERS AND STANDING COMMITTEES

### ELECTED BY THE COUNCIL

PRESIDENT: GEORGE LEONARD SCHADT, Springfield.

PRESIDENT-ELECT: ROGER I. LEE, Boston.

VICE-PRESIDENT: PEIRCE H. LEAVITT, Brockton.

SECRETARY: MICHAEL A. TIGHE, Lowell.

TREASURER: CHARLES S. BUTLER, Boston.

ASSISTANT TREASURER: ELIOT HUBBARD, JR., Cambridge.

ORATOR: EDWARD P. BAGG, Holyoke.

### DELEGATES TO HOUSE OF DELEGATES (A.)

DAVID D. SCANNELL, Jamaica Plain; DWIG O'HARA, Waltham; CHARLES E. MONGE, Somerville; WALTER G. PHIPPEN, Salem; JOHN M. BIRNIE, Springfield; RICHARD MILLER, Boston.

Executive Offices, 8 Fenway, Boston. Telephone, Ken. 2094

COMMITTEE ON PUBLICATIONS — *Chairman*, Richard M. Smith; James P. O'Hare, Conrad Wesselhoeft, William B. Breed, Oliver Cope.

COMMITTEE ON APPOINTMENTS — *Chairman*, Gordon M. Morrison\*; Roy J. Heffernan, Sidney C. Wiggin,\* Robert H. Barker,\* Richard I. Smith.\*

COMMITTEE ON ETHICS AND DISCIPLINE — *Chairman*, Ralph R. Stratton; William J. Brickley, Allen G. Rice, Fred R. Jovett, Archibald R. Gardner.

COMMITTEE ON MEDICAL EDUCATION — *Chairman*, Robert T. Monroe; George D. Henderson, Leland S. McKittrick, Chester S. Keefer, Isaac R. Jankelson.

COMMITTEE ON MEMBERSHIP — *Chairman*, Harlan F. Newton; John E. Fish, Peirce H. Leavitt, A. William Reggio, Leland S. McKittrick, William H. Allen,† H. Quimby Gallupe,† Albert E. Parkhurst.†

\*Ad interim.

†Representing the supervising physicians.

COMMITTEE ON PUBLIC HEALTH — *Chairman*, Francis P. Denny; Gerald N. Hoet, Herbert L. Lombard, Hilbert F. Day, Frank W. Marlow, Jr.

COMMITTEE ON MEDICAL DEFENSE — *Chairman*, Arthur W. Allen; Edwin D. Gaud, William R. Morrison, Horatio Rogers, George S. Reynolds.

COMMITTEE ON SOCIETY HEADQUARTERS — *Chairman*, William H. Robey; Charles Mixer, John M. Birnie, Charles S. Butler, Erwin C. Miller.

COMMITTEE ON FINANCE — *Chairman*, John Homans; Ernest L. Hunt, Charles Wilinsky, Edward J. O'Brien, Jr., Peer P. Johnson.

COMMITTEE ON INDUSTRIAL HEALTH — *Chairman*, Dwight O'Hara; Joseph C. A. Daniel L. Lynch, Henry C. Marble, Joseph C. Merriam, Thomas L. Shipman, John N. Shirley.

## OFFICERS OF THE SECTIONS

### ELECTED BY THE SECTIONS

The street addresses may be obtained from the *Directory of Officers and Fellows*.

#### SECTION OF MEDICINE

*Chairman*, Laurence D. Chapin, Springfield; *secretary*, Richard P. Stetson, Chestnut Hill.

#### SECTION OF SURGERY

*Chairman*, James C. McCann, Worcester; *secretary*, Oliver Cope, Cambridge.  
EXECUTIVE COMMITTEE — Ernest M. Daland, Newton and Boston (1 year); Archibald M. Fraser, Boston (2 years); Stanley J. G. Nowak, Belmont and Boston (3 years).

#### SECTION OF PEDIATRICS

*Chairman*, James Marvin Baty, Belmont and Brookline; *secretary*, Gerald N. Hoeffel, Cambridge.

#### SECTION OF OBSTETRICS AND GYNECOLOGY

*Chairman*, Christopher J. Duncan, Waban; *vice-chairman*, Arthur F. G. Edgel, Springfield; *secretary*, George Van S. Smith, Brookline.

#### SECTION OF RADIOLOGY

*Chairman*, Joseph H. Marks, Newton; *secretary*, Stanley A. Wilson, Malden.

#### SECTION OF PHYSIOTHERAPY

*Chairman*, Henry A. Tadgell, Winchester; *secretary*, Wilmot L. Marden, Concord.

#### SECTION OF DERMATOLOGY AND SYPHILOLOGY

*Chairman*, J. Harper Blaisdell, Winchester; *secretary*, G. Marshall, Crawfordsville, Lincoln.

## OFFICERS OF THE DISTRICT MEDICAL SOCIETIES FOR 1942-1943

### ELECTED BY THE DISTRICT MEDICAL SOCIETIES AT THEIR ANNUAL MEETINGS IN 1942

The street addresses may be obtained from the *Directory of Officers and Fellows*.

BARNSTABLE — *President*, Julius C. Kelley, Pocasset; *vice-president*, Joseph N. Kelly, Orleans; *secretary*, Donald E. Higgins, Cotuit; *treasurer*, Harold F. Rowley, Harwich Port; *librarian*, Carroll H. Keene, Chatham; *executive councilor*, William D. Kinney, Osterville.

BERKSHIRE — *President*, George M. Shipton, Pittsfield; *vice-president*, Charles T. Leslie, Pittsfield; *secretary*, George S. Reynolds, Pittsfield; *treasurer*, Clement F. Kernan, Pittsfield; *executive councilor*, John J. Boland, Pittsfield.

BRISTOL NORTH — *President*, John A. Reese, Attleboro; *vice-president*, Joseph L. Murphy, Taunton; *secretary*, William H. Swift, Taunton; *treasurer*, Joseph V. Chaigny, Taunton; *executive councilor*, William H. Allen, Mansfield.

BRISTOL SOUTH — *President*, Charles A. Bonney, Jr., New Bedford; *vice-president*, Edward F. Shay, Fall River; *secretary and treasurer*, Albert H. Sterns, New Bedford; *executive councilor*, Edwin D. Gardner, New Bedford.

ESSEX NORTH — *President*, Elmer S. Bagnall, Groveland; *vice-president*, Robert E. Blais, Amesbury; *secretary*, Harold R. Kurth, Lawrence; *treasurer*, Guy L. Richardson, Haverhill; *executive councilor*, Frank W. Snow, Newburyport.

ESSEX SOUTH — *President*, DeWitt S. Clark, Salem; *vice-president*, James A. Dumas, Lynn; *secretary*, H. Graham Pope, Swampscott; *treasurer*, Andrew Nichols, III, Danvers; *executive councilor*, Loring Grimes, Swampscott.

FRANKLIN — *President*, Arthur W. Hayes, Greenfield; *vice-president*, Kenneth H. Rice, South Deerfield; *secretary and treasurer*, Harry L. Craft, Ashfield; *executive councilor*, Frederick J. Barnard, Greenfield.

HAMDEN — *President*, George L. Steele, Springfield; *vice-president*, Edward A. Keowit, Holyoke; *secretary and treasurer*, Wayne C. Barnes, Springfield; *executive councilor*, George L. Steele, Springfield.

HAMPSHIRE — *President*, Mary P. Snook, Chesterfield; *vice-president*, Arthur N. Ball, Northampton; *secretary and treasurer*, Joseph R. Hobbs, Williamsburg; *librarian*, Abbie M. O'Keefe, Northampton; *executive councilor*, L. Beverly Pond, Easthampton.

MIDDLESEX EAST — *President*, Charles W. DeWolf, Wakefield; *vice-president*, Roger M. Burgoyne, Winchester; *secretary*, Kenneth L. MacLachlan, Melrose; *treasurer*, Albert E. Small, Melrose; *librarian*, Angelo L. Maietta, Winchendon; *executive councilor*, Kenneth L. MacLachlan, Melrose.

MIDDLESEX NORTH — *President*, Michael A. Tighe, Lowell; *vice-president*, Hiet M. Larrabee, Tewksbury; *secretary*, Raoul L. Drapeau, Dracut; *treasurer*, Mason Bryant, Lowell; *executive councilor*, William M. Collins, Lowell.

MIDDLESEX SOUTH — *President*, Hilbert F. Day, Cambridge; *vice-president*, Har G. Giddings, Newton Centre; *secretary*, Alexander A. Levi, Newton Centre; *treasurer*, Eliot Hubbard, Jr., Cambridge; *orator*, Edward D. Churchill, Belmont; *executive councilor*, Dwight O'Hara, Waltham.

NORFOLK — *President*, John A. Seth, Dorchester; *vice-president*, John C. Fisher, West Roxbury; *secretary*, Timothy F. P. Lyons, Milton; *treasurer*, Frederic Reis, Jamaica Plain; *executive councilor*, Carl Bearse, Boston.

NORFOLK SOUTH — *President*, Walter L. Sargent, Quincy; *vice-president*, Geo V. Higgins, Randolph; *secretary and librarian*, Henry H. A. Blyth, Quincy; *treasurer*, Frank W. Crawford, Holbrook; *executive councilor*, Daniel E. Ream, Quincy.

PLYMOUTH — *President*, Charles D. McCann, Brockton; *vice-president*, Edward Perry, Middleboro; *secretary*, Ralph C. McLeod, Brockton; *treasurer*, Alton Hurlburt, East Bridgewater; *librarian*, John H. Weller, Bridgewater; *executive councilor*, Peirce H. Leavitt, Brockton.

SUFFOLK — *President*, James P. O'Hara, Boston; *vice-president*, Howard A. Boston; *secretary*, Hollis L. Albright, Boston; *treasurer*, Richard S. Edlin, Boston; *executive councilor*, Donald Munro, Boston.

WORCESTER — *President*, Gordon Berry, Worcester; *vice-president*, Andrew O'Connell, Worcester; *secretary*, Julius J. Tegeler, Worcester; *treasurer*, Edward Disbrow, Worcester; *librarian emeritus*, Albert C. Geichell, Worcester; *executive councilor*, Ralph S. Perkins, Worcester.

WORCESTER NORTH — *President*, Harold C. Arey, Gardner; *vice-president*, Howard D. Bone, Gardner; *secretary*, Edward A. Adams, Fitchburg; *treasurer*, Frederick Thompson, Jr., Fitchburg; *executive councilor*, John J. Curley, Leominster.

# INDEX

## TO

### The New England Journal of Medicine

Volume 226, January 1, 1942 to June 25, 1942

#### PAGES ACCORDING TO WEEKLY ISSUES

PAGES	No	DATE	PAGES	No	DATE
1-36	1	Jan 1	547-588	14	Apr 2
37-80	2	Jan 8	589-628	15	Apr 9
81-126	3	Jan 15	629-670	16	Apr 16
127-172	4	Jan 22	671-706	17	Apr 23
173-212	5	Jan 29	707-744	18	Apr 30
213-250	6	Feb 5	745-786	19	May 7
251-290	7	Feb 12	787-840	20	May 14
291-322	8	Feb 19	841-872	21	May 21
323-366	9	Feb 26	873-902	22	May 28
"	"	Mar 5	903-936	23	June 4
"	"	Mar 12	937-968	24	June 11
"	"	Mar 19	969-1012	25	June 18
"	"	Mar 26	1013-1056	26	June 25

#### BOOK REVIEWERS\*

ADAMS, RALPH	LANF, C. GUY	RESNIK, JOSEPH
BALLARD, JAMES F.	LIUM, ROLF	ROBEY, WILLIAM H.
BUTLER, CHARLES S.	LOMBARD, HERBERT L.	ROOT, HOWARD F.
COLE, EDWIN M.	LYON, ARTHUR BATES	SAVITZ, HARRY A.
DOWNING, JOHN G.	MANSFIELD, JAMES S.	SPECTOR, BENJAMIN
EDWARDS, EDWARD A.	MCCARTHY, FRANCIS P.	SPRAGUE, HOWARD B.
FAULKNER, JAMES M.	MINER, LEROY M. S.	THOMAS, JACKSON M.
GOLDBERG, BERNARD I.	MOORE, MERRILL	VIETS, HENRY R.
GREEN, ROBERT M.	MORRISON, HYMAN	WARREN, SHIELDS
HERTZ, SAUL	O'HARA, DWIGHT	WHITE, PAUL D.
JANEWAY, CHARLES A.	PAINTER, CHARLES F.	WIGGIN, SIDNEY C.
KUHNS, JOHN G.	PIJOAN, MICHEL	
LAHEY, FRANK H.	POPE, ALTON S.	

\*This list includes only those whose work appears in this volume

#### KEY TO ABBREVIATIONS

c — correspondence  
cr — case record  
e — editorial

MMS — Massachusetts Medical Society  
me — medical eponym  
mr — meeting report

misc — miscellany  
n — notice  
o — obituary

\* — original article

# OFFICERS AND STANDING COMMITTEES

## ELECTED BY THE COUNCIL

PRESIDENT GEORGE LEONARD SCHADT, Springfield

PRESIDENT ELECT ROGER I LEE, Boston

VICE PRESIDENT PEIRCE H LEAVITT, Brockton

SECRETARY MICHAEL A TIGHE, Lowell

TREASURER CHARLES S BUTLER, Boston

ASSISTANT TREASURER ELIOT HUBBARD, JR., Cambridge

ORATOR EDWARD P. BAGG, Holyoke

DELEGATES TO HOUSE OF DELEGATES (A M A)  
DAVID D SCANNELL, Jamaica Plain, DWIGHT O'HARA, Waltham CHARLES E WONG, Somerville, WALTER G PHIPPEN, Salem, JOHN M BIRNIE, Springfield, RICHARD MILLER, Boston

Executive Offices, 8 Fenway, Boston. Telephone, Ken. 2094

COMMITTEE ON PUBLICATIONS — *Chairman*, Richard M Smith, James P O'Hare, Conrad Wesselhoeft, William B Breed Oliver Cope

COMMITTEE ON ARRANGEMENTS — *Chairman* Gordon M Morrison\*, Roy J Heffernan, Sidney C Wiggin\*, Robert H Barker\*, Richard I Smith\*

COMMITTEE ON ETHICS AND DISCIPLINE — *Chairman*, Ralph R Stratton, William J Brickley, Allen G Rice Fred R Joutet, Archibald R Gardner

COMMITTEE ON MEDICAL EDUCATION — *Chairman*, Robert T Monroe George D Henderson, Leland S McKittrick, Chester S Keefer, Isaac R Jankelson

COMMITTEE ON MEMBERSHIP — *Chairman*, Harlan F Newton, John E Fish Peirce H Leavitt, A William Reggio, Leland S McKittrick, William H Allen,† H Quimby Gallupe,† Albert E Parkhurst†

\*Ad interim

†Representing the superintendents of Medical Colleges

Journal

## OFFICERS OF THE SECTIONS

### ELECTED BY THE SECTIONS

The street addresses may be obtained from the *Directory of Officers and Fellows*.

#### SECTION OF MEDICINE

*Chairman*, Laurence D Chapin, Springfield, *secretary*, Richard P Stetson, Chestnut Hill

#### SECTION OF SURGERY

*Chairman*, James C McCann Worcester, *secretary*, Oliver Cope, Cambridge  
EXECUTIVE COMMITTEE — Ernest M Daland Newton and Boston (1 year), Archibald M Fraser, Boston (2 years), Stanley J G Nowak Belmont and Boston (3 years)

#### SECTION OF PEDIATRICS

*Chairman*, James Marvin Baty, Belmont and Brookline, *secretary*, Gerald N. Hoeffel, Cambridge

#### SECTION OF OBSTETRICS AND GYNECOLOGY

*Chairman*, Christopher J. Duncan, Waban, *vice chairman*, Arthur F. G Edgels Springfield, *secretary*, George Van S Smith, Brookline

#### SECTION OF RADIOLOGY

*Chairman*, Joseph H Marks, Newton, *secretary*, Stanley A Wilson, Marshfield

#### SECTION OF PHYSIOTHERAPY

*Chairman*, Henry A Tadgell, Winchester, *secretary*, Wilmot L Mardey, Lynn

#### SECTION OF DERMATOLOGY AND SYPHILOLOGY

*Chairman*, J. Harper Blaisdell, Winchester, *secretary*, G Marshall Lincoln

## OFFICERS OF THE DISTRICT MEDICAL SOCIETIES FOR 1942-1943

### ELECTED BY THE DISTRICT MEDICAL SOCIETIES AT THEIR ANNUAL MEETINGS IN 1942

The street addresses may be obtained from the *Directory of Officers and Fellows*.

BARNSTABLE — *President*, Julius G Kelley, Pocasset, *vice president*, Joseph N Kelly, Orleans, *secretary*, Donald E Higgins Cotuit, *treasurer*, Harold F Rowley, Harwich Port, *librarian*, Carroll H Keene Chatham, *executive counselor*, William D Kinney, Osterville

BERKSHIRE — *President*, George M Shipton, Pittsfield, *vice president*, Charles T Leslie, Pittsfield, *secretary*, George S Reynolds, Pittsfield, *treasurer*, Clement F. Kernan, Pittsfield, *executive counselor*, John J Boland, Pittsfield

BRISTOL NORTH — *President*, John A Reese Attleboro, *vice president*, Joseph L Murphy, Taunton, *secretary*, William H Swift, Taunton, *treasurer*, Joseph V. Chatigny, Taunton, *executive counselor*, William H Allen, Mansfield

BRISTOL SOUTH — *President*, Charles A Bonney, Jr., New Bedford, *vice president*, Edward F Shay, Fall River, *secretary* and *treasurer*, Albert H Sterns, New Bedford, *executive counselor*, Edwin D Gardner, New Bedford

ESSEX NORTH — *President*, Elmer S Bagnall, Groveland, *vice president*, Robert E Blais, Amesbury, *secretary*, Harold R Kurth, Lawrence, *treasurer*, Guy L Richardson, Haverhill, *executive counselor*, Frank W Snow, Newburyport

ESSEX SOUTH — *President*, DeWitt S Clark, Salem, *vice president*, James A Dumas, Lynn, *secretary*, H Graham Pope, Swampscott, *treasurer*, Andrew Nichols, III, Danvers, *executive counselor*, Loring Grimes, Swampscott

FRANKLIN — *President*, Arthur W Hayes Greenfield, *vice president*, Kenneth H Rice, South Deerfield, *secretary* and *treasurer*, Harry L Craft, Ashfield, *executive counselor*, Frederick J Barnard Greenfield

HAMDEN — *President*, George L Steele Springfield, *vice president*, Edward A Knowlton, Holyoke, *secretary* and *treasurer*, Wayne C Barnes, Springfield, *executive counselor*, George L Steele, Springfield

HAMPSHIRE — *President*, Mary P Snook, Chesterfield, *vice president*, Arthur N Ball, Northampton, *secretary* and *treasurer*, Joseph R Hobbs, Williamsburg, *librarian*, Abbie M O'Keefe, Northampton, *executive counselor*, L Beverly Pond Easthampton

MIDDLESEX EAST — *President*, Charles W DeWolf Wakefield, *vice president*, Roger M Burgoyne, Winchester, *secretary*, Kenneth L MacLachlan, Melrose, *treasurer*, Albert E Small, Melrose, *librarian*, Angelo L Maletta, Woburn, *executive counselor*, Kenneth L MacLachlan, Melrose

MIDDLESEX NORTH — *President*, Michael A Tighe, Lowell, *vice president*, Herbert M Larabee, Tewksbury, *secretary*, Raoul L Drapeau, Dracut, *treasurer*, Mason J Bryant, Lowell, *executive counselor*, William M Collins, Lowell

MIDDLESEX SOUTH — *President*, Hilbert F Day, Cambridge, *vice president*, Harold G Giddings, Newton Centre, *secretary*, Alexander A Levi, Newton Centre, *treasurer*, Eliot Hubbard, Jr., Cambridge, *orator*, Edward D Churchill, Belmont, *executive counselor*, Dwight O'Hara, Waltham

NORFOLK — *President*, John A Seth, Dorchester, *vice president*, John C Fisher, West Roxbury, *secretary*, Timothy F. P Lyons, Milton, *treasurer*, Freden Reis, Jamaica Plain, *executive counselor*, Carl Bearse, Boston

NORFOLK SOUTH — *President*, Walter L Sargent, Quincy, *vice president*, Gell V Higgins, Randolph, *secretary* and *librarian*, Henry H A Blyth, Quincy, *treasurer*, Frank W Crawford, Holbrook, *executive counselor*, Daniel B Reis, Quincy

PLYMOUTH — *President*, Charles D McCann, Brockton, *vice president*, Edward P Perry, Middleboro, *secretary*, Ralph C McLeod, Brockton, *treasurer*, Alton Hurlburt, East Bridgewater, *librarian*, John H Weller, Bridgewater, *executive counselor*, Peirce H Leavitt, Brockton

SUFFOLK — *President*, James P O'Hare, Boston, *vice president*, Howard J Boston, *secretary*, Hollis L Albright, Boston, *treasurer*, Richard S Edgerly, Boston, *executive counselor*, Donald Munro, Boston

WORCESTER — *President*, Gordon Berry, Worcester, *vice president*, Andrew P O'Connell, Worcester, *secretary*, Julius J Tegelberg, Worcester, *treasurer*, Edward P Disbrow, Worcester, *librarian*, Emeritus, Albert C Getchell, Worcester, *executive counselor*, Ralph S Perkins, Worcester

WORCESTER NORTH — *President*, Harold C Arcey, Gardner, *vice president*, Howard D Bone Gardner, *secretary*, Edward A Adams Fitchburg, *treasurer*, Frederick H Thompson Jr., Fitchburg, *executive counselor*, John J Curley, Leominster

- Collier, H E 872  
 Colwell, E M 126  
 Communicable Disease Control [Anderson & Arnstein] 670  
 Comroe, B I 511  
 Davidson, L S P 250  
 Davis M M 172  
 De Jongh, T W 967  
 Development Diagnosis [Gesell & Amatruda] 512  
 Dietetics for Clinician [Bridges] 126  
 Diseases of the Nails [Pardo-Castello] 627  
 Diseases of Thyroid Gland [Hertzler] 365  
 Doctor Takes a Holiday An autobiographical fragment [McKibbin Harper] 36  
 Drinker, C K 366  
 Ebersen, Frederick 588  
 Effective Living [Turner & McHose] 935  
 Electrocardiography, Including an Atlas of Electrocardiograms [Katz] 80  
 Electrocardiography in Practice [Graybiel & White] 36  
 Ellinger, F 1012  
 Endocrine Function of Iodine [Salter] 250  
 Endocrinology The glands and their functions [Hoskins] 936  
 Epilepsy and Cerebral Localization [Penfield & Erickson] 936  
 Erickson, T C 936  
 Essentials of \_\_\_\_\_ [Full] 706  
 Essentials of \_\_\_\_\_ [Katz] 80  
 Essential Exercises in \_\_\_\_\_ [Katz] 80  
 Fatal Partners War and disease [Major] 366  
 Field Service Notes for Regimental Officers [Colwell] 126  
 Foot and Ankle [Lewin] 467  
 Foundations of Neuropsychiatry [Cobb] 172  
 Garceau, O 35  
 Geckeler, G D 512  
 Gesell, A 512  
 Gilman A 250  
 Goodfolk, C 967  
 Goldrumer K 935  
 Goodman L 250  
 Graybiel, A 36  
 Grollman A 1012  
 Gross R E 840  
 Handbook of Communicable Diseases [Top] 967  
 Harley G W 212  
 Harris E H R 79, 172  
 Harris, H J 512  
 Hawley, E E 968  
 Health and Doctors 366  
 Health Resorts of U S S R 1056  
 Henry, G W 902  
 Hertzler A E 365  
 Hess J H 1056  
 History of Medical Psychology [Zilboorg & Henry] 902  
 Holmes W H 249  
 Holtzman, D F 706  
 Hoskins, R G 936  
 How to Prevent Goiter [Bram] 212  
 Hull E 706  
 Hydrotherapy in Psychiatric Hospitals [Wright] 79  
 Infant Nutrition A textbook of infant feeding for students and practitioners of medicine [Marriott] 1056  
 Infantile Paralysis Lecture I Poliomyelitis (Vanderbilt Univ.) 36  
 Introduction to Medical Science [Boyd] 936  
 Johnstone R T 968  
 Joki, E 967  
 Katon S R 706  
 Katz L N 80  
 Kolmer, J A 288  
 Ladd W E 840  
 Leaders of Medicine [Kagan] 706  
 Leavell H R 627  
 Lectures on War Neuroses [Ross] 872  
 Lewin, P 467  
 Loewenberg, S A 288  
 Lundeen E C 1056  
 Lymphatics Lymph and Lymphoid Tissue [Drinker & Yoffey] 366  
 Major, R H 366  
 Malignant Disease and its Treatment by Radium [Cade] 705  
 Man Who Lived for Tomorrow A biography of William Hillock Park [Oliver] 840  
 Manual of Bandaging Splinting and Strapping [Thornike Jr] 410  
 Marriott W McK 1056  
 McBee I A 706  
 McHose E 935  
 McKibbin Harper, M 36  
 Medical Diagnosis and Symptomatology [Loewenberg] 288  
 Microbes Challenge [Ebersen] 588  
 Microbes Which Help or Destroy Us [Allen & others] 706  
 Modern Dermatology and Syphilology [Becker & Obermayer] 80  
 Moore S 935  
 Native African Medicine, with special reference to its practice in the Mingo tribe of Liberia [Harley] 212  
 Needham J G 902  
 1940 Year Book of Public Health 172  
 Obermayer M E 80  
 Observations Made During Epidemic of Measles on Faroe Islands in Year 1846 [Panum] 628  
 Occupational Diseases Diagnosis medicolegal aspects and treatment [Johnstone] 968  
 O'Hara D 840  
 Oliver, W W 840  
 Oral Pathology [Thoma] 322  
 Orr, H W 935  
 Outlines of Industrial Medical Practice [Collier] 872  
 Panum, P L 628  
 Pardee, H E B 36  
 Pardo-Castello, V 627  
 Pathology of Oral Cavity [Cahn] 366  
 Penfield W 936  
 Pharmacological Basis of Therapeutics [Goodman & Gilman] 250  
 Pharmacology of Anesthetic Drugs [Adrian] 628  
 Political Life of American Medical Association [Garceau] 35  
 Premature Infant Its medical and nursing care [Hess & Lundeen] 1056  
 Primer for Diabetic Patients [Wilder] 79  
 Proceedings of the Charaka Club Vol 1 967  
 Randolph, C R 902  
 Research Conference on Cause and Prevention of Dental Caries 250  
 Rheumatic Fever in New Haven 670  
 Ross T A 872  
 Ruch T C 706  
 Salter, W T 250  
 School Health Services [Walker & Randolph] 902

## SUBJECT INDEX

## A

- ABDOMINAL SURGERY [Allen] \*57  
 ABDOMINOSCROTAL hydrocele [Prather] \*255  
 ACROMEGALY and diabetes mellitus, retinal lipemia and visual disturbances associated with [Igersheimer] \*754  
 ADDISON'S DISEASE, optimal dosage and reciprocal relation of desoxycorticosterone acetate and sodium in [McGavack] \*547  
 ADENOCARCINOMA, primary, in a Meckel's diverticulum [Albright & Sprague] \*142  
 AIR SUPREMACY, medicine and [Fulton] 873 - MMS  
 ALCOHOL addicts, pyruvic acid studies in peripheral neuropathy of [Wortis & others] \*376  
 ALCOHOLISM, chronic, protein of cerebrospinal fluid in patients with [Trowbridge & Secunda] \*195  
   a medical and community problem 833 - c  
 ALLERGY: Serum reactions, with particular reference to prevention and treatment of tetanus [Rackemann] \*726  
 AMERICAN INSTITUTE FOR PSYCHOANALYSIS 664 - c  
   [Coriat & Kaufman] 838 - c  
 AMERICAN MEDICAL ASSOCIATION, political life of [Means] 466 - c  
 AMERICAN TRUDEAU SOCIETY 168 - misc  
 "AMERICAN WAY OF LIFE" 400 - c  
   (See New lamps for old) 504 - c  
 ANEMIA, some remarks on therapy for [Castle] 903 - MMS  
 ANESTHESIA, regional, its use in obstetrics and gynecology [Waters] \*380  
 ANEURYSM, dissecting, of ascending aorta [Breed & others] 456 - cr  
   of descending aorta probably syphilitic, with rupture [Dieuaide & others] 352 - cr  
 ANEURYSMS, dissecting, of aorta [Ludwig] 273 - cr  
 ANGINA PECTORIS, treatment of, with testosterone propionate [Lesser] \*51  
 ANIMAL experimentation, treatment of deafness in light of recent: otology [Lurie] \*886  
 ANKLE joint, fractures around [Darrach] \*333  
 ANNUAL MEETING 777 - c; (report) 929 - c  
 ANTHRAX: Report of a fatal case involving the cutaneous and gastrointestinal systems [MacDonald] \*949  
 AORTIC ANEURYSM, hematemesis due to rupture of [Kaplan] \*984  
 APPENDICEAL PERITONITIS, statistical study of six hundred and seventy-one cases of [Faxon & Rogers] Introduction, \*707; Part I, \*708; Part II, \*745  
 APPENDICITIS and acute gastroenteritis in college men, differential diagnosis of acute [Quigley & Contratto] \*787  
 ARGYRIA confused with heart disease [Levine & Smith] \*682  
 ARMED FORCES, protection for physicians in [Day] 838 - c  
 ARTIFICIAL radioactive isotopes in medicine and biology [Ross] \*854  
 AUSCULTATION of abdomen in intestinal obstruction, value of [Stevens] \*87 (See Acute intestinal obstruction) 115 - c  
 AUTHORS, medical bibliography of Sixteenth Century 1002 - c  
 AUTONOMIC nervous system, surgery of [Smithwick] \*605

## B

- BARBITURATES, regulation of sale of 895 - c  
 BARRETT, JOHN T. (See Notes) 899 - misc  
 BEGG SOCIETY 1006 - misc

- BEHAVIOR disorders, electroencephalographic studies dren presenting [Secunda & Finley] \*850  
 BIBLIOGRAPHY, medical, of sixteenth-century authors I (HENRY JACOB) BIGELOW MEDAL, PRESENTATION c introductory remarks [Walker] \*513  
   Presentation of medal [Cheever] \*514  
   Present-Day Surgery of Pancreas [Whipple] \*51  
 BILE-DUCT reconstruction with vitallium tubes [Clut (KENNETH D.) BLACKFAN 1883-1941, 358 - o  
 BLAST and concussion in present war [Fulton] \*1  
 BLOOD-PROCUREMENT SERVICE 31 - c  
 BOARD OF REGISTRATION IN MEDICINE, Change in 46  
 BOCK, ARLIE V. (See Notes) 546 - misc  
 BOOK REVIEWS  
   Abdominal Surgery of Infancy and Childhood. & Gross] 840  
   Abnormal Speech [Boome & Harries] 172  
   About Ourselves [Needham] 902  
   Adriani, J. 628  
   Allen, P. W. 706  
   Amatruda, C. S. 512  
   America Organizes Medicine [Davis] 172  
   Anderson, G. W. 670  
   Anderson, I. A. 250  
   Arnstein, M. G. 670  
   Art and Science of Nutrition [Hawley & Carden] 511  
   Arthritis and Allied Conditions [Comroe] 511  
   Ashman, R. 706  
   Autonomic Nervous System [White & Smithwic  
   Bacillary and Rickettsial Infections, Acute and C [Holmes] 250  
   Becker, S. W. 80  
   Bibliographia primatologica [Ruch] 706  
   Biologic Fundamentals of Radiation Therapy [El 1012  
   Biological Symposia: Vol. 111, 968  
   Blair, V. P. 935  
   Boas, E. P. 1056  
   Boome, E. J. 172  
   Boyd, W. 936  
   Brackett, C. A. 322  
   Bram, I. 212  
   Bridges, M. A. 126  
   Brucellosis (Undulant Fever), Clinical and Sub [Harris] 512  
   Butt, H. R. 366  
   Byars, L. T. 935  
   Cade, S. 705  
   Cahn, L. R. 366  
   Cancer of Face and Mouth [Blair & others] 935  
   Carden, G. 968  
   Cardiac Classics 670  
   Cardiac Clinics: A Mayo Clinic monograph [W 935  
   Clinical Aspects of Electrocardiogram, Including diac Arrhythmias [Pardee] 36  
   Clinical and Experimental Investigations on the C Functions and Their Hormonal Regulation [Zo 628  
   Clinical Immunology, Biotherapy and Chemother: Diagnosis, Prevention and Treatment of D [Kolmer & Tuft] 288  
   Clinical Practice in Infectious Diseases for Stu Practitioners and Medical Officers [Harries] 79  
   Cluver, E. H. 967  
   Cobb, S. 172

- CRIPPLED CHILDREN, care of [Huber] 622 - MMS  
 CURABLE treatment of spastic children [Denhoff & Bradley] \*411

## D

- DAMESHER, WILLIAM (See Notes) 837 - misc  
 DANGERS of indirect contact with tuberculous patients 898 - misc  
 DEAFNESS, treatment of, in light of recent animal experimentation otology [Laurie] \*886

## DEATHS

- Baldwin, Leon K 786  
 Barnes, Francis J 786  
 Benson Charles S 786  
 Blackfan, Kenneth D 358 - o  
 Bonney, Robert 585  
 Bragg, Francis A 286  
 Breen, John J 871  
 Brown, George A 544  
 Butler, Francis J 1003  
 Byrnes, John P 165  
 Celce, Frank F 786  
 Clarke, Inez L 544  
 Cook, James H 623  
 Cox, Stanley C 1003  
 Crane, Clarence 702  
 Dalton, Charles H 317  
 Damon, Arthur L 786  
 Daudelin, Alfred 318  
 Delahanty, William J 897  
 Deming Robert M 318  
 Diez, M Luise 667  
 Dow, David C 932  
 Downey, Hugh J 247  
 Durgin, Edward C 786  
 Eaton, Charles A 1052  
 Field, Henry M 897  
 Freund, Ernest 623  
 Gilin, William 667  
 Goodwin, Harold C 409  
 Hartwell, William W 466  
 Hersam, Norman P 165, 834  
 Higgins, James H 835  
 Hinds William H 545  
 Ladd, Maynard 508  
 LaFrance, Albert J 545  
 Lord Frederick T 869 - o  
 Lourie, Osip R 286  
 Mallory, Frank B 279 - o  
 McGuinness, John F 1052  
 Meedy, Joseph A 623  
 Mutty, Lawrence T 545  
 Neff, Irwin H 932  
 O Leary, Cornelius J 897  
 Paine, Mortimer H 124  
 Perry, Sherman 702  
 Peters, Andrew 545  
 Popoff, Constantine 963  
 Potter, A Carleton 247  
 Reed, Victor A 466  
 Rodrick, Albert F 836  
 Sanborn, Benjamin E 318  
 Sears, Henry F 124  
 Sise, Lincoln F 836  
 Stowell Edmund C 124  
 Swift Walter B 836  
 Ten Broeck, Stanton J 286  
 Wakefield, A Paul 317

- Walker, John B 702  
 Watson, Francis S 836  
 Webber, Norman B 545, 871  
 Weiss, Somr 247, 505 - o  
 Wheeler, John B 871  
 Williams, David L 1004  
 Wood, Henry A 401 - o

- DEFENSE, family nutrition and [Diez] 543 - MMS  
 DIABETES MELLITUS, retinal lipemia and visual disturbances associated with acromegaly and [Igersheimer] \*754  
 DIFFERENTIAL diagnosis of acute appendicitis and acute gastroenteritis in college men [Quigley & Contratto] \*787  
 DIPHTHERIA antitoxin [Jakmau] 624 - c  
 DISSECTING aneurysm of aorta with slight hemorrhage into mediastinum pericardium and pleural cavities [Bland & others] 828 - cr  
 DISSECTION in treatment of carcinoma, evaluation of regional lymph node [Taylor] \*367  
 DIVERTICULITIS of sigmoid [Young & others] 695 - cr  
 DYSMENORRHEA essential [Fremont Smith] \*795

## E

- ECHINOCOCCAL CYST [Ulfelder & others] 538 - cr  
 EDITORIALS  
 Alcoholism Medical and community problem 833  
 American Institute for Psychoanalysis 664  
 American Way of Life '400  
 Annual meeting 777, (report) 929  
 Barbiturates, regulation of sale of 895  
 Blood procurement service 31  
 Board of Registration in Medicine, change in, 464  
 Challenge to federal, state and local health departments 312  
 Civilian casualties, services for care of 69  
 Civilian defense 464  
 Civilian defense, responsibilities of hospitals in matters of 278  
 Commonwealth Fund 930  
 Compliment 868  
 Control of cancer 577  
 Early rising after operations 576  
 Financing war 541  
 Hold Fast That Which Is Good 739  
 Hospital facilities 505  
 Huntington Hospital 70  
 Industrial hygiene and war 962  
 Industrial nurse 542  
 Intestinal obstruction, acute 115  
 Kenny method of treatment of infantile paralysis 700  
 Malpractice insurance for physicians in military service 700  
 Massachusetts licenses general hospitals 1001  
 Maternal mortality 1050  
 Medical bibliography of sixteenth-century authors 1002  
 Medical education and war 206  
 Medical officers, immediate need for 961  
 Medical officers recruiting board 929  
 Medical service plans 619  
 National emergency recommendations to medical students and physicians concerning the 242  
 National foundation for infantile paralysis 620  
 New lamps for old 504  
 Nutrition, science of 278  
 'Physicians, speeding production of' 244  
 (Ella Sachs) Plotz Foundation 778

- Pneumonia, treatment of, in home 867  
 Procurement and Assignment Service 162, 206, 356, 739, 777, 832  
*Pulse* — and future 896  
 Sanatorium care for rheumatic children 401  
 Selectees, examination of 357  
 Selectees and their physical fitness 663  
 Service, call to 31  
 Typhoid carriers 740  
 United War Fund Campaign 162, 242  
 War and venereal disease 114  
 (Karel Frederik) Wenckebach 313  
 (Casey) Wood (1856–1942) and American Medicine 1051  
 ENDOCARDITIS, enterococcal [Skinner & Edwards] \*8  
 ELECTROCARDIOGRAM, use and abuse of the, in medical practice [Marvin] \*213  
 ELECTROENCEPHALOGRAPHIC studies in children presenting behavior disorders [Secunda & Finley] \*850  
 EMBOLISM of middle cerebral and posterior cerebral arteries [White & Castleman] 110 – cr  
 EMERGENCY FIELD STATIONS, supplies to. (See Medical and Surgical Relief Committee of America) 837 – misc  
 EMERGENCY, recommendations to medical students and physicians concerning national 242 – e  
 ENDOCARDITIS, bacterial (type 7 pneumococcus) [Ropes & others] 923 – cr  
 ENDOCRINOLOGY: Treatment of abnormalities of anterior pituitary gland [Aub & Karnofsky] \*759  
 ENDOSCOPY [Benedict] \*449  
 ENTERITIS regional [Warren & Miller] \*589  
     regional, Meckel's diverticulum [Urmy] 307 – cr  
 ENTEROBIASIS, trichinosis and: their importance in New England [Augustine] \*488  
 ENTEROCOCCAL endocarditis [Skinner & Edwards] \*8  
 EPONYMS, MEDICAL  
     Ludwig's angina 32  
     Lugol's solution 71  
     Malpighian corpuscles 163  
     McBurney's point 116  
     Ménière's disease 207  
     Milroy's disease 244  
     Möbius's sign 283  
     Morton's toe 314  
     Murphy button 359  
     Murphy drip 465  
     Murphy maneuver 402  
     De Musset sign 506  
     Negri bodies 542  
     Neisser's diplococcus 578  
     Nélaton's line 620  
     Niemann–Pick disease 665  
     Oppenheim's sign 702  
     Oppler–Boas bacilli 741  
     Osgood–Schlatter's disease 778  
     Paget's disease (osteitis deformans) 834  
     Paget's disease (precancerous eczema) 870  
     Parry's disease 897  
     Pasteur treatment 931  
     Pfeiffer bacillus 962  
     Pick's disease 1003  
     Von Pirquet reaction 1052  
 EVALUATION of regional lymph-node dissection in treatment of carcinoma [Taylor] \*367  
 EVANS MEMORIAL HOSPITAL, Nov. 21, 511 – mr; Jan. 23, 965 – mr; Mar. 23, 468 – n  
 (ROBERT DAWSON) EVANS MEMORIAL LECTURE, Mar. 27, 467 – n

- EWING'S TUMOR [Roberts] \*90  
 EXAMINATION of selectees 357 – e

## F

- FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY, Mar. 31 to Apr. 4, 468 – n  
 FEMUR, fractures of [Van Gorder] \*526  
 FINANCING war 541 – e  
 "FOOT-STRAIN," important etiologic factor in so-called [Osgood] \*552  
 FOREIGN-BODY perforation of ileum [Sweet & others] 891 – cr  
 FRACTURES around ankle joint [Darrach] \*333  
     of femur [Van Gorder] \*526  
 FURMETHIDE (furfuryl-trimethyl-ammonium iodide) action of, on bladder in patients with primary retention following surgery on rectum [Lipton & others] \*138

## G

- GALLUPE, H. QUIMBY (See Change in Board of Registration in Medicine) 464 – e  
 GANGRENE of Meckel's diverticulum [Sarris] 239 – cr  
 GIANT-CELL tumor of humerus [Simmons & others] 571 – cr  
 GLOMERULONEPHRITIS, acute and chronic [Butler & others] 1046 – cr  
     chronic [Graybiel & others] 28 – cr  
     subacute [Richardson & others] 459 – cr  
 GONOCOCCAL infections, chemotherapy in [Cox] \*184  
 GOVERNOR'S address [Blood] \*294  
 GREATER BOSTON MEDICAL SOCIETY, Nov. 4, 321, 839; Feb. 3, 1053 – mr  
 GYNECOLOGY: Endometriosis [Meigs] \*147

## H

- HAMARTOMA of spleen [Sweet & Warren] \*757  
 HANDICAPPED child, medical social service for [Cannon] 33 – MMS  
 HAND–SCHUELLER–CHRISTIAN syndrome [Mueller & Farb] 392 – cr  
 HARVARD MEDICAL SCHOOL appointments (See Note) 872 – misc  
     awards (See Notes) 668 – misc  
     promotions (See Notes) 837 – misc  
     and Dental School, appointments (See Notes) 899 – misc  
     Dental School and School of Dental Medicine, appointments (See Notes) 287 – misc  
 HARVARD MEDICAL SOCIETY, Oct. 14, 170; Nov. 12, 51 Dec. 9, 705 – mr  
 HARVEY MEDICAL SOCIETY, Jan. 30, 966 – mr  
 HEALTH departments, challenge to federal, state and local 312 – e  
 HEART action, clinical aspects of paroxysmal rapid [Woll] \*640  
     disease, argyria confused with [Levine & Smith] \*6  
     disease, laboratory aids in diagnosis and prognosis [Ellis] \*798  
 HEMATEMESIS due to rupture of aortic aneurysm [Kaplan] \*984  
     paradoxical [Hinman] \*417  
 HEMATOLOGY: anemia, with particular reference to hemolytic syndrome [Dameshek] \*339  
     diseases other than anemia [Dameshek] \*383  
 HEMOTHORAX complicated by infection with *Clostridium welchii* [Lynch & Strieder] \*685

- EMPHYSEMA [Stellar] \*336  
 ENTERO, left inguinal, with acute Meckel's diverticulitis and peritonitis [Lum & Ladd] \*15  
 EVANS, NORMAN PAUL, 1884-1942, in memoriam 834  
 FRACTURES ununited [Hermann] \*601  
 FLEISCHER (See Presidential address [Dolloff] 974)  
 GIDDIST, What Which Is Good? 739 - c  
 GYNASTIC FACILITIES 505 - c  
 GYNOSTIC, typhoid fever in [Jakmauh] 742 - c  
 GYNOSTIC  
 Hospital Lying in Hospital, Journal Club, Oct. 30, 320 -  
 mr, Mar 18, 467 - n  
 Jarney Hospital Journal Club, Jan 8, 899 - mr, Mar 14, 467 - n  
 Jekler Nival Hospital, Nov 14, 668 - mr  
 Jans Memorial Hospital, Nov 21, 511 - mr Jan 23, 965 - mr, Mar 23, 465 - n  
 Jans Memorial Hospital, Dec 3, 587 - mr, Mar 19, 468 - n  
 Massachusetts General Hospital, Hospital Research Council Mar 24, 468 - n  
 Newbury State Hospital and Infirmary 318 - misc  
 United States Naval Hospital, Jan 9, 626 - mr  
 Hospitals, Massachusetts licenses general 1001 - c  
 responsibilities of, in matters of civilian defense 278 - c  
 rules and regulations for licensing [Jakmauh] 1006 - c  
 JUNCTION Hospital 70 - c  
 JUNCTION, congenital, in lower half of double kidney [Feyder & Deming] \*220  
 JUNCTION, chest pain in patients with mitral stenosis with particular reference to so-called [Burgess & Ellis] \*937  
 JUNCTION of heart, cause unknown [White & others] 395 - cr

## I

- IDIOPATHIC HYPERTROPHY and dilatation of heart [Gravibel & others] 158 - cr  
 INDUSTRIAL HYGIENE and war 962 - c  
 INDUSTRIAL nurse 542 - c  
 INFANTILE PARALYSIS, Kenny method of treatment of 700 - c  
 International foundation for 620 - c  
 Infection of portion of great omentum [Hamlin & others] 237 - cr  
 INGUINAL hernia, left, with acute Meckel's diverticulitis and peritonitis [Lum & Ladd] \*15  
 INJURY, malpractice, for physicians in military service 700 - c  
 medical care costs, recommendations of subcommittee on prepaid 118  
 medical care costs, report of special committee on prepayment 436 - MMS  
 military malpractice [Morrison] 704 - c  
 Intestinal obstruction, acute 115 - c  
 Intestinal obstruction, value of auscultation of abdomen in [Stevens] \*87  
 See acute intestinal obstruction 115 - c  
 INJURY, contracture, Volkmann's [Fosic] \*671  
 TOPES, artificial radioactive, in medicine and biology, [Ross] \*854

## J

- JUNCTION, familial nonhemolytic [Curry & others] \*909  
 Jans Memorial Hospital, Dec. 3, 587 - mr, Mar 19, 468 - n  
 Jans M (See Note) 1006 - misc  
 JANS, conservation of scholarly 362 - misc

## K

- KIDNEYS and their treatment [Nison] \*883  
 KIDNEY method of treatment of infantile paralysis 700 - c  
 KING, LEOPOLD F (See Notes) 899 - misc

## L

- LICHEN PLANUS Diagnosis, etiology and treatment [Bird] \*986  
 LIPOSARCOMA of thigh [Wallace] 204 - cr  
 LIVER, cirrhosis of, complicated by persistent right hydrothorax and ascites [Frothingham] \*679  
 cirrhosis of, portal, type undetermined [Talbot & others] 992 - cr  
 comparison of blood prothrombin levels with standard function tests in diseases of [White & others] \*327  
 with hemochromatosis, association of primary neoplasm of [Saward] \*264  
 LORD FREDERICK T, 1875-1941, 869 - o  
 LUDWIG'S ANGINA 32 - me  
 LUDWIG'S SOLUTION 71 - me  
 LUNG LIPOSARCOMA, multiple, of jejunum and ileum [Hyden & others] 959 - cr

## M

- MALORY FRANK BUFER An appreciation 279 - o  
 MALPRACTICE CORPUSCLES 163 - me  
 MALPRACTICE INSURANCE military [Morrison] 704 - c  
 for physicians in military service 700 - c  
 MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH in civilian defense, role of [Jakmauh] 507 - MMS  
 MASSACHUSETTS GENERAL HOSPITAL, Hospital Research Council, Mar 24 468 - n  
 MASSACHUSETTS hospitals, rules and regulations for licensing [Jakmauh] 1006 - c  
 licenses general hospitals 1001 - c  
 MASSACHUSETTS MEDICAL SOCIETY  
 Anemia, some remarks on therapy for [Castle] 903  
 Annual meeting 777 - c, (report) 929 - c  
 Applicants for fellowship 403  
 By laws, committee to revise 578  
 Child inner world of [Moore] 408  
 Childhood abdominal surgery [Hudson] 360  
 Civilian defense, role of Massachusetts Department of Public Health in [Jakmauh] 507  
 Committee on Arrangements (program substitutions) 871

## COMMITTEE ON MATERNAL WELFARE

- Abortion placenta, associated with hysterectomy and followed by death 506  
 Acute inversion of uterus, causing hemorrhage and death 666  
 Acute inversion of uterus resulting in fetal hemorrhage 1052  
 Analysis of causes of maternal death in Massachusetts during 1940, 71, 164  
 Causes of maternal death in Massachusetts during 1940, 120, 207, 245, 254, 314  
 Complete separation of placenta, followed by death 466  
 Curettage causing perforation of uterus and fatal sepsis 578  
 Diabetes, fatal, in pregnancy 835  
 Eclampsia, followed by fatal cerebral hemorrhage 543  
 Fatal eclampsia and cerebral hemorrhage 1003  
 Hydranmios followed by post partum hemorrhage, hysterectomy and death 702



- Myelogenous leukemia, fatal in pregnancy 932  
 Obstetric routines 360  
 Pernicious vomiting, fatal in pregnancy 897  
 Placenta, retained, followed by uterine and tubal abscesses and death 621  
 Post-partum hemorrhage followed by sepsis and death 402  
 Resolution to establish 32  
 Rupture in tubal pregnancy causing fatal peritonitis 870  
 Rupture in tubal pregnancy, followed by death 779  
 Toxemia followed by anuria and death 962  
 Toxemic pregnancy, followed by unsuccessful operative delivery and death 741
- 
- Committee on Postgraduate Instruction, May 27, 786  
 Congress on Medical Education and Licensure, Feb. 14-17 [Fitz] 407  
 Council, Feb. 4, proceedings of 421; stated meeting of 117  
 Council, Apr. 15, special meeting of 543; proceedings of 805  
 Council, May 25, annual meeting of 779  
 Council, May 25 and 26, proceedings of 1028  
 Crippled children, care of [Huber] 622  
 Employment of interns by War Department (See office of secretary) 835  
 Golf tournament, annual 786  
 Insurance, medical care costs, recommendations of subcommittee on prepaid 118  
 Insurance, medical care costs, report of special committee on prepayment 436  
 Irradiation in treatment of cancer of breast [O'Brien & McDonald] 17  
 McCann report 436  
 Medical care costs insurance, recommendations of subcommittee on prepaid 118  
 Medical education, list of schools and colleges approved by committee on 119  
 Medical social service for handicapped child [Cannon] 33  
 Medicine and air supremacy [Fulton] 873  
 (Frank L.) Morse retirement 360  
 Nutrition and defense, family [Diez] 543  
 Oration, annual. Some remarks on therapy for anemia [Castle] 903  
 Postgraduate extension courses (program—winter sessions) 121  
 Problems of tuberculosis under wartime conditions [Pope] 666  
 Program of annual meeting, May 25, 26 and 27, 782  
 SHATTUCK LECTURE: Medicine and air supremacy [Fulton] 873  
 Tax-supported medical care, report of subcommittee on 117  
 Treasurer's notice 286  
 Treasurer's report 621  
 Tuberculosis in children [Smith] 315
- MASSACHUSETTS MEDICO-LEGAL SOCIETY, May 26, 786—n  
 MASSACHUSETTS, reclassification of reported cases of tuberculosis in [Welch & Zacks] \*1020  
 results of fifteen years of cancer-control program in [Lombard & Macdonald] \*81  
 résumé of communicable diseases, Nov. 210; Dec. 319; Jan. 362; Feb. 624; Mar. 837; May 1053—misc  
 MASSACHUSETTS TUBERCULOSIS LEAGUE, Mar. 26, 468—n  
 MASSACHUSETTS TUMOR DIAGNOSIS SERVICE 212—misc  
 MASSACHUSETTS, typhus fever in [Hayes & Gill] \*916
- MATERNAL mortality 1050—c  
 welfare, committee on 32—MMS  
 MCBURNLEY'S POINT 116—me  
 MCCANN REPORT 436—MMS  
 MECKEL'S DIVERTICULUM, primary adenocarcinoma in [bright & Sprague] \*142  
 MEDICAL bibliography of sixteenth-century authors 1002  
 care costs insurance, recommendations of subcommittee on prepaid 118—MMS  
 discharges from military service [Flicker & Coleman] \*945  
 education, list of schools and colleges approved by committee on 119—MMS  
 education and war 206—c  
 officers, immediate need for 961—c  
 Officers' Recruiting Board (location of) 929—c  
 service plans 619—c  
 social service for handicapped child [Cannon] 33—MMS  
 MEDICAL AND SURGICAL RELIEF COMMITTEE OF AMERICA 837—misc  
 MEDICINE and air supremacy [Fulton] 873—MMS  
 MÉNIÈRE'S DISEASE 207—me  
 MENINGITIS, pneumococcal [Dowling & others] \*1015  
 MENSTRUAL BLOOD, so-called "coagulation defect" in [Lerner & others] \*481  
 MENTAL disorders associated with pregnancy and puerperium [Ordway & McIntire] \*969  
 MIDDLESEX SOUTH and Massachusetts medicine [Giddings] \*37  
 MIDDLESEX UNIVERSITY (See Notes) 287, 546, 837, 965—misc  
 MILIARY TUBERCULOSIS, generalized [Baker & Hampton] 773—cr  
 MILITARY malpractice insurance [Morrison] 704—c  
 service, malpractice insurance for physicians in 700—c  
 service, medical discharges from [Flicker & Coleman] \*945  
 MILROY'S DISEASE 244—me  
 MITRAL stenosis with particular reference to so-called "hypercyanotic angina," chest pain in patients with [Burgess & Ellis] \*937  
 MOEBIUS'S SIGN 283—me  
 MORSE, FRANK L. (See Retirement) 360—MMS  
 MORTALITY, maternal 1050—c  
 summary for 1941, annual 287—misc  
 MORTON'S TOE 314—me  
 MUCOCLE of appendix [McKittrick & others] 202—cr  
 MUELLER, J. HOWARD (See Notes) 899—misc  
 MUMPS [Wesselhoef] \*530  
 MURPHY BUTTON 359—me  
 MURPHY DRIP 465—me  
 MURPHY MANEUVER 402—me  
 DE MUSSET Sign 506—me
- N
- NATIONAL FOUNDATION FOR INFANTILE PARALYSIS 620—c  
 NATIONAL PHYSICIANS' COMMITTEE [Weld] \*84  
 NEGRI BODIES 542—me  
 NEISSER'S DIPLOCOCCUS 578—me  
 NÉLATON'S LINE 620—me  
 NEOPLASM of liver with hemochromatosis, association of primary [Saward] \*264  
 NEPHRITIS, acute glomerular [Kranes & others] 535—cr  
 NERVOUS system, surgery of autonomic [Smithwick] \*605  
 NEURITIS, peripheral, following the administration of glucose sulfapyridine compound [Sugar] \*1022  
 New England Journal of Medicine (See Compliment) 868—c

1. . . . . particular reference to hemo-  
339

- Hematology: Diseases other than anemia [Dameshek] 383  
 Heterogeneous renal disorders [Talbot] 228  
 Laboratory aids in diagnosis and prognosis of heart disease [Ellis] 798  
 Lichen planus [Baird] 986  
 Mumps [Wesselhoeft] 530  
 Nutritional deficiencies in relation to digestive tract [Jones] 563  
 Obstetrics, medical aspects of [Smith] 21  
 Ophthalmology [Waite] 1023  
 Otology: Treatment of deafness in light of recent animal experimentation [Lurie] 886  
 Psychiatry: Neuroses in war [Williams] 302  
 Renal-function tests [Talbot] 197  
 Surgery of autonomic nervous system [Smithwick] 605  
 Syphilis [Lane & Crawford] 97  
 Toxic reactions following sulfonamide treatment [Keefer] 266  
 Trichinosis and enterobiasis: Their importance in New England [Augustine] 488  
 Vascular disorders of extremities [Homans] 917, 951  
 PROMIN in treatment of tuberculosis 1004—misc  
 PROTEIN of cerebrospinal fluid in patients with chronic alcoholism [Trowbridge & Secunda] \*195  
 PROTHROMBIN levels, comparison of blood, with standard function tests in diseases of liver [White & others] \*327  
 PSYCHIATRIC aspects of ulcerative colitis [Daniels] \*178  
 "aspects of ulcerative colitis" [Fischbein] 509—c  
 PSYCHIATRY (See Presidential address [Doloff] 974)  
 PSYCHIATRY: Neuroses in war [Williams] \*302  
 PUBLICITY, distorted [Sieve] 126—c  
 PULMONARY embolism and thrombosis [Talbot] 66—c  
 tuberculosis and pregnancy [Baker & Ward] \*224  
 Pulse — and future 896—c  
 PYELONEPHRITIS, recurrent, during pregnancy [Prather & Sewall] \*291  
 PYRUVIC acid studies in peripheral neuropathy of alcohol addicts [Wortis & others] \*376

## R

- RADIOACTIVE isotopes, artificial, in medicine and biology [Ross] \*854  
 RADIO BROADCASTS  
 Childhood abdominal surgery [Hudson] 360—MMS  
 Crippled children, care of [Huber] 622—MMS  
 Inner world of child [Moore] 408—MMS  
 Medical social service for handicapped child [Cannon] 33—MMS  
 Nutrition and defense, family [Diez] 543  
 Role of Massachusetts Department of Public Health in Civilian Defense [Jakmauh] 507—MMS  
 Tuberculosis in Children [Smith] 315—MMS  
 Tuberculosis under wartime conditions, problems of [Pope] 666—MMS  
 READING, neurologic aspects of defects in speech and [Cole] \*977  
 REFUGEE physicians [Zanfagna] 1006—c  
 RENAL cyst, use of aspirating needle in diagnosis of solitary [Wheeler] \*55  
 disorders, heterogeneous [Talbot] \*228  
 function tests [Talbot] \*197  
 RETINAL lipemia and visual disturbances associated with acromegaly and diabetes mellitus [Igersheimer] \*754  
 RHEUMATIC children, sanatorium care for 401—c  
 ROSS, MATHEW (See Annual prize subscription) 872—misc

- RULES and regulations for licensing hospitals [Jakmauh] 1006—c  
 RUSHMORE, STEPHEN (See Notes) 287—misc

## S

- Salmonella suispestifer* infection in Boston [Goulder & others] \*127  
 SANATORIUM care for rheumatic children 401—c  
 SARCOID? [Lerman & others] 657—c  
 SARCOMA of breast [Rogers & Flo] \*841  
 SCHERING award winners 871—misc  
 SCHOOL lunches 211—misc  
 SELECTEES and their physical fitness 663—c  
 SEROLOGIC tests for syphilis [Jakmauh] 509—c  
 SHAKING chills in typhoid fever [Aisner & Waitzkin] \*3  
 SHATTUCK LECTURE: Medicine and air supremacy [Fulton] 873—MMS  
 SMALL-BOWEL obstruction due to phytobezoar [Smith & others] 864—c  
 SOCIETIES  
 Begg Society 1006—misc  
 Boston Orthopedic Club, Nov. 17, 624; Dec. 15, 7 Jan. 19, 932; Feb. 16, 1055—mr  
 Carney Hospital Journal Club, Jan. 8, 899—mr  
 Federation of American Societies for Experimental Biology, Mar. 31 to Apr. 4, 468—n  
 Greater Boston Medical Society, Nov. 4, 321; Jan. 6, 839; Feb. 3, 1053—mr  
 Harvard Medical Society, Oct. 14, 170; Nov. 12, 510 Dec. 9, 705—mr  
 Harvey Medical Society, Jan. 30, 966—mr  
 Journal Club, Boston Lying-in Hospital, Oct. 30, 320—mr; Mar. 18, 467—n  
 Massachusetts Medico-Legal Society, May 26, 786—n  
 Massachusetts Tuberculosis League, Mar. 26, 468—n  
 New England Pathological Society, Oct. 16, 363; Nov. 20, 704; Jan. 13, 248; Jan. 15, 901—mr; Mar. 15, 468—n  
 New England Pediatric Society, Jan. 14, 872—mr  
 New England Roentgen Ray Society, Mar. 20, 468—n  
 New England Society of Physical Medicine, Jan. 21, 934—mr; Mar. 18, 468—n; June 3 (See Notes) 965—misc  
 Suffolk District Medical Society, Oct. 22, 319—mr  
 SPASTIC CHILDREN, curare treatment of [Denhoff & Bradley] \*411  
 SPEECH and reading, neurologic aspects of defects in [Cole] \*977  
 SPINAL-NERVE ROOTS, degeneration of [Means & others] 347—c  
 STATISTICAL study of six hundred and seventy-one cases of appendiceal peritonitis [Faxon & Rogers] Introduction, \*707; Part I, \*708; Part II, \*745  
 STILBESTROL, use of, in relief of essential dysmenorrhea [Sturgis] \*371  
 STRONG, RICHARD P. (See Notes) 624—misc  
 SUBSCRIPTION, annual prize 872—misc  
 SUFFOLK DISTRICT MEDICAL SOCIETY, Oct. 22, 319—mr  
 SULFADIAZINE in man, pharmacodynamics of [Ratish & others] \*596  
 SULFANILAMIDE, toxic effects from intraperitoneal use of [Lesses & Starr] \*558  
 powder spray [Phaneuf & Stevens] 668—c  
 SULFAPYRIDINE compound, peripheral neuritis following administration of glucose [Sugar] \*1022  
 SULFATHIAZOLE ointment in treatment of pyogenic dermatoses [Glicklich] \*981

study of one hundred and thirty two cases of pneumonia treated in home with [Rosenthal & others] \*845  
 ALFONAMINE treatment, toxic reactions following [Keefer] \*266  
 APPLIES to emergency field stations (See Medical and Surgical Relief Committee of America) 837 - misc  
 JERFERY of pancreas, present day [Whipple] \*515  
 PHILIS [Lane & Crawford] \*97  
 serologic tests for [Jakmauh] 509 - c

## T

TANNIC ACID to liver necrosis occurring in burns, relation of [Wells & others] \*629  
 T-SUPPORTED medical care, report of subcommittee on 117 - MMS  
 ELANGIETASIS, hereditary [Stellar] \*336  
 ESTOSTERONE propionate, treatment of mammary pain and secretion with [Nathanson & others] \*323  
 EWASBURY STATE HOSPITAL AND INFIRMARY 318 - misc  
 IORACOPLASTY, results of 409 - misc  
 RAUMATIC emphysema of mediastinum [Sinclair Loutie] 170 - c  
 obstruction of main bronchus [Tyson & Lyle] \*192  
 RICHMOND and enterobiosis Their importance in New England [Augustine] \*488  
 UCHOMOVAGINITIS treatment of, with acetarsone trimpons [Meigs] \*562  
 UBERCULOSIS in children [Smith] 315 - MMS  
 of bronchus [Churchill & others] 825 - cr  
 in civilians and in members of armed forces, elimination of 545 - misc  
 in Massachusetts, reclassification of reported cases of [Welch & Zacks] \*1020  
 is found when looked for 703 - misc  
 and pregnancy, pulmonary [Baker & Ward] \*224  
 problems of, under wartime conditions [Pope] 666 - MMS

promin in treatment of 1004 - misc  
 UBERCULOUS meningitis [Penfield & others] 1044 - cr  
 patients dangers of indirect contact with 898 - misc  
 peritonitis [Adams & others] 25 - cr  
 UFTS COLLEGE MEDICAL SCHOOL  
 (See Annual prize subscription) 872 - misc  
 Alumni Association Mar 25, 467 - n  
 (See Notes) 1053 - misc  
 UTOR DIAGNOSIS SERVICE, Massachusetts 212 - misc  
 YPHOID carriers 740 - c  
 cholecystitis, unrecognized, as source of hospital infections [Rubenstein] \*722  
 YPHOID FEVER, chemotherapy in [Kattwink] \*419  
 in hospital personnel [Jakmauh] 742 - c  
 shaking chills in [Aisner & Waitzkin] \*301  
 YPHUS FEVER in Massachusetts [Hayes & Gill] \*916

## U

ICERATIVE COLITIS psychiatric aspects of [Daniels] \*178  
 NITED STATES NAVAL HOSPITAL, Jan 9 626 - misc  
 NITED WAR FUND CAMPAIGN 162, 242 - c  
 PJOHN COMPANY (See Vice president of pharmaceutical firm dies) 837 - misc  
 RNARY tract, recent advances with chemotherapy in treatment of infections of [Cook] \*187  
 se of sulbesterol in relief of essential dysmenorrhea [Sturgis] \*371

## V

VASCULAR disorders of extremities [Homans] \*917, \*951  
 VENEREAL disease, war and 114 - c  
 VETERANS ADMINISTRATION, physicians for [Adams] 742 - c  
 VIETS HENRY R (See Compliment) 868 - c  
 VITAMIN B<sub>1</sub> and endurance [Karpovich & Millman] \*881  
 VITAMIN C and wound healing I Experimental wounds in guinea pigs II Ascorbic acid content and tensile strength of healing wounds in human beings [Bartlett & others] \*469, \*474  
 VITAMIN DEFICIENCY, chemical measurement and control of clinical [Salter] \*649, \*688  
 VOIKMANN'S ischemic contracture [Foisie] \*671

## W

## WAR ACTIVITIES

## CIVILIAN DEFENSE

Blood and plasma banks 963  
 Chemical warfare course 871  
 Clarification of function of Red Cross and civilian defense units 1005  
 Deputy medical director 34  
 First aid for air raid casualties 586  
 Hospitals to be reimbursed for care of civilian casualties 703  
 Massachusetts Committee on Public Safety (new appointments) 1053  
 Medical Handbook No 2 Organization for Emergency Medical Services, for the Care of Civilian Casualties 72  
 Nursing service for the war 508  
 Plan to establish blood banks 742  
 Publications, new 898  
 Red Cross chapters, relation of, to defense councils 317  
 State hospital officer 836  
 United States Office of Civilian Defense 210  
 War Gases Textbook on 545  
 Evacuation system manual No 2 165  
 Eyes, decontamination, after exposure to lewisite and mustard gas 667  
 General Hospital No 5, 209  
 Selective Service System 466  
 United States Army, Base Hospital No 6, 932  
 Officers 34, 124, 209  
 United States Navy officers 247, 286  
 Opportunity for appointments of premedical and medical students as ensigns H V (P), United States Naval Reserve 248

## WAR, blast and concussion in present [Fulton] \*1

financing 541 - c  
 medical education and 206 - c  
 and venereal disease 114 - c  
 (SONA) WFEISS 1899-1942, 505 - o  
 (KAREL FREDERIK) WFNKEBACH 313 - c  
 WHITE PAUL D (See Notes) 872 - misc  
 (CASEY) WOOD (1856-1942) and American medicine 1051 - c  
 (HENRY AUSTIN) WOOD, 1855-1942 401 - o  
 WOODBRIDGE, PHILIP D (See Notes) 1053 - misc  
 WOUND healing (See Vitamin C) \*469, \*474  
 WOUNDS and Burns, study and treatment of contaminated [Faxon] 410 - c

## AUTHOR INDEX

## A

ADAMS, F. D. 25—cr  
 ADAMS, W. 742—c  
 AISNER, M. \*301  
 ALBRIGHT, H. L. \*142  
 ALLEN, A. W. \*57; 496, 864, 891—cr  
 ALTSCHULE, M. D. \*138  
 APPEL, B. \*912  
 AUB, J. C. \*759  
 AUGUSTINE, D. L. \*488  
 AYER, J. B. 613—cr

## B

BAIRD, P. C., JR. \*986  
 BAKER, M. P. 773—cr  
 BAKER, R. H. \*224  
 BARTLETT, M. K. 272—cr; \*469, \*474  
 BEASER, S. B. \*138  
 BENEDICT, E. B. 25—cr; \*449; 538, 825—cr  
 BLAND, E. F. 154, 395, 828—cr  
 BLOOD, R. O. \*294  
 BOYER, N. H. \*217  
 BRADLEY, C. \*411  
 BRAILEY, A. G. 659, 734—cr  
 BREED, W. B. 456, 957—cr  
 BUEDING, E. \*376  
 BULLOWA, J. G. M. \*596  
 BURCHENAL, J. H. \*1013  
 BURGESS, A. M., JR. \*937  
 BUTLER, A. M. 861, 997, 1046—cr

## C

CANNON, I. M. 33—MMS  
 CASTLE, W. B. 903—MMS  
 CASTLEMAN, B. 28, 110—cr  
 CHFEVER, D. \*514, \*517  
 CHURCHILL, E. D. 825—cr  
 CLUTE, H. M. \*484  
 COLBY, F. 861, 923—cr  
 COLE, E. M. \*977  
 COLEMAN, O. H. \*945  
 COLL, J. J. \*629  
 CONTRATTO, A. W. \*787  
 COOK, E. N. \*187  
 CORIAT, I. H. 838—c  
 COX, O. F. \*184  
 CRAWFORD, G. M. \*97  
 CURRY, J. J. \*909

## D

DAMESHEK, W. \*339, \*383  
 DANIELS, G. E. \*178  
 DARRACH, W. \*333, \*594  
 DAUER, C. C. \*1015  
 DAVENPORT, L. F. 64, 769—cr  
 DAY, H. F. 838—c  
 DEMING, C. L. \*220  
 DENHOFF, E. \*411  
 DEUTSCH, E. \*327  
 DIEUAIDE, F. R. 352, 992—cr  
 DIEZ, M. L. 543—MMS  
 DOCK, W. 105—cr

DOLLOFF, C. H. \*974  
 DOWLING, H. F. \*1015

## E

EDWARDS, J. E. \*8  
 ELLIS, L. B. \*798, \*937

## F

FARBER, S. 392, 1046—cr  
 FAXON, H. H. 697—cr; \*707, \*745  
 FAXON, N. W. 410—c  
 FELDMAN, H. A. \*1015  
 FEYDER, S. \*220  
 FINLEY, K. H. \*850  
 FISCHBEIN, L. 509—c  
 FITZ, R. 407—MMS  
 FITZHUGH, G. 923—cr  
 FLICKER, D. J. \*945  
 FLO, S. \*841  
 FOISIE, P. S. \*671  
 FOX, H. J. \*1013  
 FREMONT-SMITH, M. 456, 613—cr; \*795  
 FROTHINGHAM, J. R. \*679  
 FULTON, J. F. \*1; 873—MMS

## G

GARLAND, J. 997—cr  
 GIDDINGS, H. G. \*37  
 GILL, C. E. \*916  
 GLENDY, R. 736—cr  
 GLICKLICH, E. A. \*981  
 GOULDER, N. E. \*127  
 GRAHAM, J. R. 926—cr  
 GRAYBIEL, A. 28, 158—cr  
 GREENWALT, T. J. \*909

## H

HAMLIN, E. 237, 496—cr  
 HAMPTON, A. O. 347, 657, 659, 695, 697, 769, 773, 825, 1044—cr  
 HARTMAN, C. R. \*1015  
 HAYDEN, E. P. 959—cr  
 HAYES, J. E. \*916  
 HERMANN, O. J. \*601  
 HINMAN, F., JR. \*417  
 HOLMES, G. W. 105, 154, 500, 571, 573, 734, 926—cr  
 HOMANS, J. \*917, \*951  
 HOOBLER, S. W. \*942  
 HUBER, E. G. 622—MMS  
 HUDSON, H. W., JR. 360—MMS  
 HUMPHREY, H. D. \*629

## I

IGERSHEIMER, J. \*754

## J

JAKMAUH, P. J. 124—c; 507—MMS; 509, 624, 742, 932, 1006—c  
 JANEWAY, C. A. \*127

JEFFRIES, W. 535—cr  
 JOLLIFFE, N. \*376  
 JONES, C. M. \*469, \*474, \*563; 926  
 JONES, T. D. 154—cr

## K

KAPLAN, B. \*984  
 KARNOFSKY, D. \*759  
 KARPOVICH, P. V. \*881  
 KATTWINKEL, E. E. \*419  
 KAUFMAN, M. R. 838—c  
 KEEFER, C. S. \*266  
 KINGSLAND, M. F. \*127  
 KRANES, A. 237, 535—cr  
 KUBIK, C. S. 347, 352, 613, 616—

## L

LADD, S. T. \*15  
 LANE, C. G. \*97  
 LERMAN, J. 657, 957—cr  
 LESSER, M. A. \*51  
 LESSES, M. F. \*558  
 LEVINE, S. A. \*682  
 LINGLEY, J. R. 25, 202, 237—cr  
 LINTON, R. R. 734—cr  
 LIPTON, J. J. \*138  
 LIUM, R. \*15  
 LOMBARD, H. L. \*81  
 LOWIS, S. 1044—cr  
 LOZNER, E. L. \*481  
 LUDWIG, A. O. 273—cr  
 LURIE, M. H. \*886  
 LYLE, J. S. \*192  
 LYNCH, J. P. \*685  
 LYONS, C. 861, 892, 923—cr

## M

MACCOLL, W. A. \*845  
 MACDONALD, F. A. \*81  
 MACDONALD, W. D. \*949  
 MADDOCK, S. \*327  
 MARVIN, H. M. \*213, \*251  
 McDONALD, E. 17—MMS  
 MCGAVACK, T. H. \*547  
 MCINTIRE, A. M. \*969  
 MCKITTRICK, L. S. 202—cr  
 MEANS, J. H. 347, 459, 466—cr  
 MEIGS, J. V. \*147, \*323, \*562  
 MESSINA, S. J. \*912  
 MILLER, R. H. \*589  
 MILLMAN, N. \*881  
 MOORE, M. 408—MMS  
 MORRISON, W. R. 704—c  
 MUELLER, H. L. 392—cr  
 MUELLNER, S. R. \*298

## N

NASON, L. H. \*883  
 NATHANSON, I. T. \*323

## O

O'BRIEN, F. W. 17—MMS  
 ORUWAY, M. D. \*969  
 OSGOOD, R. B. \*552

P

- PARSONS, L. 202, 309-cr; \*323;  
573-cr  
PATEK, A. J., Jr. \*1013  
PENFIELD, W. 1044-cr  
PHANEUF, M. 668-c  
POHLE, F. J. \*1013  
POPE, A. S. 666-MMS  
PRATHER, G. C. \*255, \*291  
PRATT, J. H. \*845

Q

- QUIGLEY, T. B. \*787

R

- RACKEMANN, F. M. \*726  
RATISH, H. D. \*596  
RICHARDSON, W. 25, 459, 957-cr  
ROBERTS, C. P. \*90  
ROGERS, H. \*707, \*745, \*841  
ROPER, M. W. 923-cr  
ROSENTHAL, J. \*845  
ROSS, J. F. \*854  
RUBENSTEIN, A. D. \*722  
RYAN, A. E. \*469, \*474

S

- SALTER, W. T. \*649, \*688  
SARRIS, S. P. 239-cr  
SAVARD, E. W. \*264  
SCHIAZZKI, R. 64, 959, 997-cr  
SECUNDA, L. \*195, \*850  
SEVER, J. W. \*790  
SEWALL, W. \*291  
SHACKMAN, N. H. \*596

SHULMAN, M. H. \*260

- SIEVE, B. F. 126-c  
SIGLER, L. H. \*46  
SIMMONS, C. C. \*173; 571, 573-cr  
SINCLAIR-LOUTIT, K. W. C. 170-c  
SKINNER, D. \*8  
SMITH, C. 315-MMS  
SMITH, JASPER A. \*682  
SMITH, JUDSON A. \*21  
SMITH, W. D. 828-cr  
SMITHWICK, R. H. \*605; 864-cr  
SPRAGUE, J. S. \*142  
STARR, A. \*558  
STELLAR, L. I. \*336  
STEVENS, N. C. \*87; 586, 668-c  
STRAUSS, M. B. \*1013  
STRIEDER, J. W. \*685  
STURGIS, S. H. \*371  
SUGAR, S. J. \*1022  
SWEET, R. H. \*757; 891-cr

T

- TALBOTT, J. H. 66-cr; \*197, \*228;  
861, 992-cr  
TAT, R. J. \*909  
TAYLOR, F. H. L. \*481  
TAYLOR, G. W. \*367  
TAYLOR, Z. E. \*481  
TOBEY, H. G. 573-cr  
TROWBRIDGE, E. H., Jr. \*195  
TYSON, M. D. \*192

U

- ULFELDER, H. 538-cr  
URMY, T. V. 307-cr

V

- VAN GORDER, G. \*526; 571-cr  
VIETS, H. R. \*720

W

- WAITE, J. H. \*1023  
WAITZKIN, L. \*301  
WALKER, I. J. \*513  
WALLACE, R. H. 204-cr  
WARD, A. D. \*224  
WARREN, R. \*589  
WARREN, S. \*757  
WATERS, E. G. \*380  
WELCH, C. E. 237, 500, 659-cr  
WELCH, E. J. \*1020  
WELD, S. B. \*84  
WELLS, D. B. \*629  
WESSELHOEFT, C. \*530  
WHEELER, B. C. \*55  
WHIPPLE, A. O. \*515  
WHITE, F. W. \*327  
WHITE, P. D. 28, 110, 158-cr; \*217;  
395, 736, 828-cr  
WILLIAMS, V. P. \*302  
WOLFF, L. \*640  
WOODMAN, J. B. \*636  
WORTIS, H. \*376

Y

- YOUNG, E. L. 695-cr

Z

- ZACKS, D. \*1020  
ZANFAGNA, P. E. 1006-c  
ZELLER, F. R. 992-cr



# The New England Journal of Medicine

Copyright, 1942, by the Massachusetts Medical Society

VOLUME 226

JANUARY 1, 1942

NUMBER 1

## BLAST AND CONCUSSION IN THE PRESENT WAR\*

JOHN F. FULTON, M.D.†

NEW HAVEN, CONNECTICUT

THE first definition of a bomb in the *Oxford Dictionary* is "a ball of wilde-fire." The Spaniards, it seems, quite early developed technics for burning enemy ships by projecting fire balls at their adversaries' sails and wooden decks; so that the first bombs were, strictly speaking, incendiaries. Later, mortars were developed for hurling explosive incendiaries. These explosive balls of fire became in the course of time less fiery and more highly explosive, and in the nineteenth century they came to be known as "bombshells." By the end of that century and during the last war, bombshells became just "shells," and the word "bomb" was reserved for explosives dropped from the air—or from the pocket of a discontented agitator.

The Nazis were the first to develop air bombing technics on a large scale: not only bombs of the high-explosive variety—screeching, bouncing and parachute bombs—but also "balls of wilde-fire" in the form of incendiaries, many of them diabolically arranged so that, when a firefighter attempts to smother them, they explode, showering hot burning magnesium in the faces of their victims. When attacking ships and objectives in England during the last two years, the Germans have used five types of high-explosive shells, the 50-kilo, 250-kilo and 500-kilo aerial bombs and the 500-kilo and 1000-kilo land mines.

### PHYSICAL CHARACTERISTICS OF BOMB DESTRUCTION

The 50-kilo bomb, which has been used in such profusion over the London area, produces destruction within a sharply circumscribed space for a width of 20 to 25 feet in brick dwelling houses, such as one encounters on Commonwealth Avenue or Marlborough Street, Boston; and if one of these houses were struck, one might expect, if

British example were followed, to see signs of "Business as Usual" on both sides of the 25 feet of gutted building. Similarly, when such a bomb strikes the middle of the street, it penetrates beneath the surface before exploding and then lifts up a heap of dirt over an area 20 to 30 feet in diameter and 3 to 5 feet in depth, depending on the character of the surface. The resulting crater presents a hazard to traffic. Taxicab drivers navigating in the blackout become accustomed to dropping into craters of this sort but are so skillful that they generally stop their cars when the back wheels are on the edge, quietly back out, and take another street. In England, bombing even of the 50-kilo variety is serious: since the winters are mild, the essential services are buried to a depth of only 2 or 3 feet. Almost invariably, therefore, a bombing episode in the street results in interruption of all five services—water, gas, electricity, sewerage and telephone; however, the demolition squads work with incredible speed, and generally within ten or fifteen hours all the services are repaired and the streets repaved. But all this requires a close-knit organization on the part of a dozen agencies and utilities, and I should think that the sooner such an organization is worked out on the eastern seaboard of the United States, the less the inconveniences of bombing would be felt when the time comes for the enemy to strike. We have the rich experience of the English people at our disposal. We have seen their mistakes. We have seen their magnificent reorganization on the basis of those mistakes, and I can only hope that we may profit by them.

The 250-kilo bomb creates greater havoc, but again the area of destruction is sharply circumscribed, being limited to 100 to 130 feet of four-story brick construction; if the bomb strikes in the middle of the street, the crater is 75 to 100 feet in width and 8 to 10 feet in depth. Windows may be broken at considerable distances—up to 200 or 250 yards—from the blast wave.

\*Read in part before the Maryland Psychiatric Society, Baltimore, Maryland, on Wednesday, October 8, 1941, and in modified form under the title "Bombs" before the New England Postgraduate Assembly, Cambridge, Massachusetts, October 29, 1941.

†From the Laboratory of Physiology, Yale University School of Medicine.  
15 ending Professor of Physiology, Yale University School of Medicine



The 500-kilo or 1000-pound bomb, of which, fortunately, the Germans have been able to use very few, is incredibly destructive and may, if it happens to strike favorably, demolish the greater part of a city block. The effects of the blast wave in the air and through ground-shock may topple buildings at a distance of several hundred yards, and the results of a given detonation of this size of bomb are as bizarre and unpredictable as they are destructive. Much the same thing may be said for the land mine, which, coming down by parachute, may destroy the greater part of a city block. No details concerning the so-called "super-bomb" that the British are now using are available, but it is evidently "super" in the sense of having greater weight; if it is true that the British are using bombs weighing 1 to 2 tons, the havoc wrought in closely built areas must be colossal.

### BLAST INJURIES

The first detailed histologic study of the effects on the central nervous system of blast from high explosive shells is found in a paper by Mott,<sup>1</sup> which comprises the Lettsonian Lectures delivered before the Medical Society in London in February and March, 1916. During the Civil War, Mitchell, Morehouse and Keen<sup>2</sup> described the blast syndrome in unmistakable terms, but the neuron at that time was not an entity, since staining of the nervous system to aid in histologic scrutiny had scarcely begun. Mott draws attention to Sir Anthony Bowlby's<sup>3</sup> Bradshaw Lecture, *Wounds in War*, delivered in 1915, in which he remarks:

It must also be kept in mind that the mere explosive force of the gases of a large shell exercises great powers of destruction. The expansion of the gases is alone sufficient to kill, and in the only case in my experience in which an autopsy has been made, the brain was the seat of very numerous petechial haemorrhages.

This brain, which had been in Sir Arthur Keith's custody, was turned over in 1916 to Mott, who confirmed the existence of widespread petechial hemorrhage, but who also noted changes compatible with carbon monoxide poisoning. He cites, in addition, several nonfatal cases in which the explosion of large shells caused loss of consciousness without visible external signs of injury. In all these cases, the patient in question was propelled some distance by the blast wave, but there were no external injuries to suggest a primary blow on the head. Two of these cases may be cited:

A lieutenant under my care told me that he was in a communication trench when an aerial torpedo exploded close to him. He felt a great pressure against

him; it was soft but sufficiently powerful to knock him down unconscious. He did not know how long he was unconscious, but thinks it must have been an hour. When he recovered consciousness he got up and was helped away. His head felt as if it would burst, and ever since he has had a whizzing in the left ear and dizziness. Dreams of bombs and aerial torpedoes bursting. There was no parapet to blow down on him.

An R.A.M.C. officer at the battle of Ypres had a shell explode near him. He was not hit, but lay unconscious for six hours. He recollects the shock of the shell as he went out of the dressing-room. For some days he suffered with severe headache and soreness of back of head and down the spine; the lower extremities felt heavy, but there was no loss of feeling. He had retention of urine for a day only, and around the body there was a pain like an appendix pain. He rapidly recovered.

The first case is typical of hundreds of thousands in World War I. One must recall that men were engaged in trench warfare, and that they were protected from shell fragments by being submerged in trenches but were not protected from the blast wave of a shell exploding in close proximity. On recovery, those who were actually rendered unconscious by proximity to an exploding shell complained of headache, dizziness, lethargy and inability to concentrate—in short, they exhibited all the major signs and symptoms of the postconcussion syndrome of peacetime. In the parlance of the early days of the last war, they were said to be suffering from "shell shock" (von Sarbó<sup>4</sup>).

The problem of distinguishing psychogenic war neurosis from a case of organic concussion resulting from blast is delicate and often difficult, but I agree with Myers<sup>5</sup> that such a distinction is clearly essential. In a book recently published, he distinguishes between "shell concussion," a syndrome associated with organic injury to the brain, and "shell shock," a psychogenic syndrome due to the fears and fatigue of warfare. Often, however, the two syndromes are confused (Roubinovitch<sup>6</sup>).

It is interesting to trace the term "shell shock" in the various connotations that it acquired during World War I. Late in 1914 and during 1915, a soldier was said to have suffered shell shock when he was picked up unconscious and externally uninjured in the vicinity of an exploded shell. The usage was thus synonymous with "shell concussion." Stevenson,<sup>7</sup> however, in a short paper concerning the cause of death due to high-explosive shells in unwounded men, concluded that sudden death in these circumstances results from "concussion of the brain and interference with the functions of nerve centres which are essential to life, and the interruption of which means instant death." "I have seen many men," he continued, "home from the front who have been exposed to these explosions; all their symptoms and all their accounts of their experiences tend to confirm this belief, for it is to

the less severe injuries to these centres that the symptoms of men who recover and come home all point." Later, shell shock came to be applied more particularly to the cases of functional war neurosis.

Stevenson also refers to the interesting speculation of the French civil engineer, Arnoux,<sup>8</sup> who observed an exploded aneroid in the pocket of a French officer who had been killed by proximity to an exploding shell. The aneroid was repaired, and it was found that a sudden compression of 10,000 kilos per square meter was essential to disrupt it. Arnoux put forward the theory that, following such compression, gases in the blood and tissues expanded with bubble formation, and that men were killed by sudden massive air embolism. The aneroid observation is interesting, but the attempt to explain death as due to bubble formation was far fetched, since it did not take into consideration the rate at which gases dissolve under pressure, and the slow rate at which resolution occurs when pressure is diminished.<sup>9</sup>

To Mott<sup>1</sup> must be given the credit for having first emphasized the significance and likelihood of carbon monoxide poisoning in the vicinity of an exploding shell, especially one exploding in a confined space. Oxygen is absorbed by the explosion, carbon monoxide is liberated, and many of the so-called "deaths from blast" have been shown to be due to carbon monoxide poisoning of persons unconscious or pinioned under debris. The importance of carbon monoxide poisoning has lately been re-emphasized in connection with bombing injuries among civilians in England and Germany. However this may be, death from primary blast is a clinical entity that requires close study, because of its intimate connection with concussion and with the postconcussion syndrome of neuropsychiatry.

The general subject of blast injuries is discussed under four headings: the physics of the blast wave, the effects of blast on animals, the effects of blast on man, and suggestions concerning therapy.

### Physics of Blast Wave

Bernal,<sup>10</sup> of Cambridge, England, has given the best general account of the physical characteristics of a high-explosive wave. In material of high density and small elasticity, the wave travels slowly; where density is small and elasticity great, as in air, the wave travels at great speed. The high pressures created by bomb explosions cause an enormous velocity of wave transmission in air, but the rate of movement diminishes rapidly as the wave proceeds and there is also a marked change in the shape of the wave as it progresses. The pressure in some waves rises immediately to its peak and then falls off gradually and is followed by a phase of less than atmospheric pressure, that is, the negative phase (Fig. 1). The generation of this steep-fronted wave is very similar to that of the waves that break on the seashore. The high-

pressure phase of the disturbance, which always travels faster than the low-pressure phase, gets to the front just as the top of a wave on the sea, being held back less than the base by the friction of the sand, moves forward and ultimately breaks the wave.

This steep-fronted wave, sometimes known as the "shock wave," is responsible for blast and also for some of the bizarre effects of high explosives, such as the smashing of windows and doors at a

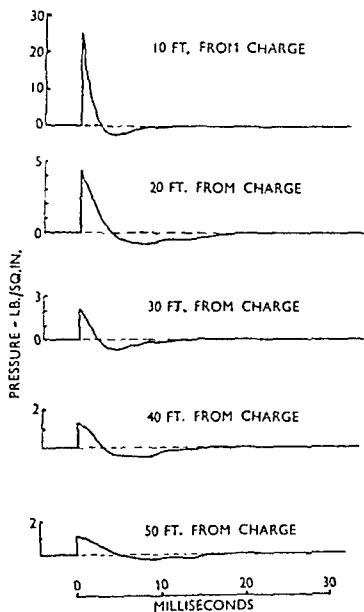


FIGURE 1. Figures Showing the Progress of a Blast Wave from a Small Charge of Powder (Bernal<sup>10</sup>).

distance. Pressure values of 5 to 10 pounds per square inch will break most windows, but blast pressures must rise to 6 atmospheres, or 100 pounds per square inch, before endangering a human being. This means that, to be injured by primary blast, a human being must be very near the site of the explosion. Zuckerman's<sup>11</sup> data on animals suggest that, at a distance of 30 feet from a 50-kilo bomb, a human being would be entirely safe from the direct effects of blast; published data concerning individual bombing episodes in which blast injuries have occurred in man support this deduction. With the large bombs, such as the 250-kilo and 500-kilo ones, the blast wave is more intense and travels farther.

Another aspect of bomb explosion concerns the blast wave in the earth, the so-called "ground

shock." Dropped from a great height, bombs generally penetrate some distance into the earth, the depth varying with the character of the surface. As previously mentioned, a 50-kilo bomb makes a crater of 20 to 30 feet in a dirt road. The sequence of events has been diagrammatically indicated by Bernal<sup>10</sup> (Fig. 2). A ground wave

difference of 2 or 3 feet often determining the question of life or death; there is a syndrome of primary shock characterized by collapse of the blood pressure in animals affected, but not killed, by the primary blast; there is complete absence of petechial hemorrhages or other intracranial lesions in the brains of animals exhibiting marked pri-

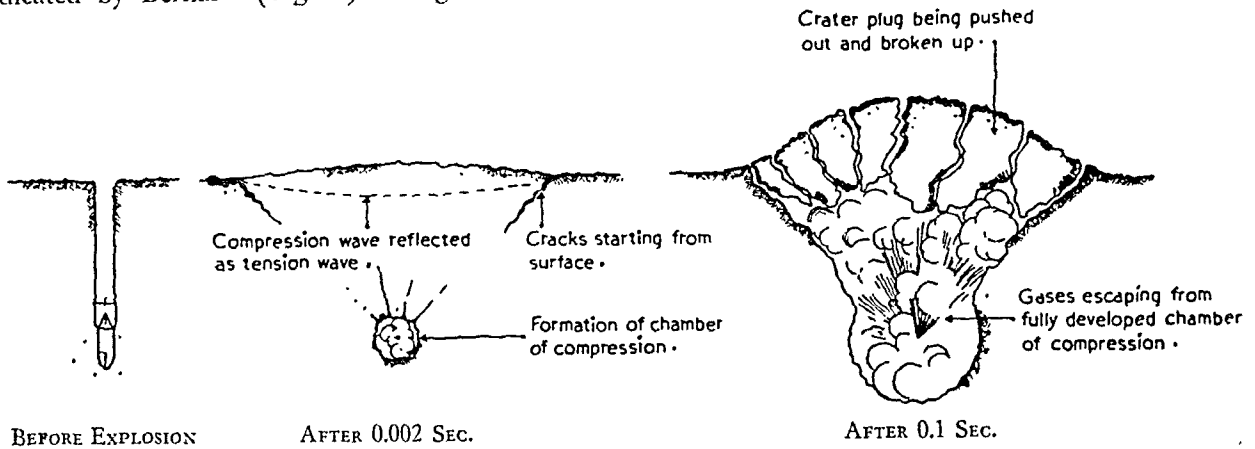


FIGURE 2. *The Series of Events Accompanying a Bomb Explosion in the Earth (Bernal<sup>10</sup>).*

has a high velocity, with an abruptly rising wave that may cause buildings to be shaken down at some distance from the site of the explosion.

#### *Effects of Blast on Animals*

The effects of primary air concussion due to shells or other explosives were not investigated experimentally until the end of World War I,<sup>12-15</sup> and to Hooker<sup>16</sup> must be given the credit for the most thorough experimental analysis as yet available. Men exposed to shell concussion, he pointed out, often developed a condition of shock that was unrelated to obvious trauma, since neither external nor internal wounds were clearly demonstrable. To investigate the phenomenon, a study was undertaken in the winter months of 1918-1919 at the Sandy Hook proving ground, with subsidy from the Committee on Shock of the National Research Council. In retrospect, it is highly significant and clearly a tribute to Hooker's insight that he regarded the condition of circulatory collapse following violent air concussion as indistinguishable from the circulatory collapse from primary shock that follows traumatic concussion in civil life. Hooker had opportunity to study the effects on frogs, cats and dogs, with the animals placed at varying distances from the muzzle of 10-inch and 12-inch guns and also from direct trinitrotoluene detonations. One dog, for example, placed 4 feet from the explosion of 4 pounds of trinitrotoluene, exhibited a fall in systolic blood pressure from 114 to 74 mm., and a fall in venous pressure from 8.7 to 6.2 mm. Hooker's studies emphasize four points: the fatal effects of primary blast occur in animals only relatively near the explosion, a

primary shock; and hemorrhagic lesions of the lungs and occasionally of other visceral organs are prevalent in animals subjected to blast. In his experience, however, the extent of the lung lesion bore little, if any, relation to the gravity of the concussion symptoms.

The experimental results of Hooker thus strongly suggest that the effects of primary blast in animals are closely similar to the effects of a blow on the head in an otherwise normal animal. He drew attention to the experimental studies of Githens and Meltzer,<sup>17</sup> and raised the question, without committing himself to an answer, whether the symptoms of air concussion were not ultimately similar to traumatic cerebral concussion.

Hooker's studies were published in 1924, but they aroused little comment. In the clinical literature during and after the war, there were many discussions of shell shock as an entity, and some authors, as already mentioned, used the term "shell concussion" to characterize symptoms resulting from primary blast.

New light on the problem has come from two groups of studies, one on blast and the other on experimental traumatic concussion of the head.

*Primary blast.* Zuckerman<sup>11, 18</sup> has given two detailed reports on the effects of primary blast in different animals, including mice, rats, guinea pigs, rabbits, cats, monkeys and pigeons. Seventy pounds of a high-explosive charge in paper containers so arranged that there would be no danger of injury from flying missiles was used as the source of the blast wave, and animals placed in well-anchored wire-mesh cages were arranged at

varying distances from the charge. As in the experiments of Hooker, there proved to be critical distance zones, which varied with the species of animal monkeys being considerably more resistant, for example, than rabbits. No monkeys were killed by a 70 pound charge at distances greater than 18 feet, and in no animal, rabbits included, were effects detectable at distances greater than 50 feet, at which the positive component of the blast wave averaged 6.3 pounds per square inch. Between 13 and 18 feet, almost all animals were killed when so placed that their body walls were affected by hydrostatic pressure alone. At these distances, the positive component of the blast wave that is, the hydrostatic pressure, varied between 126 and 63 pounds per square inch.

Between about 20 and 50 feet, no animals were killed, and those that survived showed little change in behavior. Those surviving between 18 and 21 feet often died within a few minutes to twenty-four hours after the blast; they exhibited widespread pathologic changes, the most conspicuous, as in Hooker's experiments, being hemorrhagic lesions of the lungs. But also, as in Hooker's experiment, there seemed to be no clear relation between the extent of the pulmonary lesions and the degree to which the animal had been affected by the blast wave. The pulmonary lesions are well illustrated in Zuckerman's<sup>18, 19</sup> later report.

Lesions were also found in other organs, including the epicardium of the heart, and very frequently in the large intestine, which proved to be the most susceptible, next to the lungs, to the effects of blast. The lungs, spleen and kidneys were often bruised or lacerated.

The nervous system was also carefully observed, especially in monkeys, the sections having been studied by Greenfield and also by Clark. The more important findings are summarized as follows.<sup>18</sup>

No changes were observed in the cortex, midbrain pons or medulla of monkeys subjected to pressures as high as 110 lb per square inch. On the other hand most monkeys exposed to high pressures show extradural hemorrhages in the thoracic spinal roots, which are sometimes continuous with hemorrhage along the intercostal nerves. In two animals that died, hemorrhage had occurred at the central ends of the posterior columns, and in the dorsal commissure. Furthermore, most animals have shown a zone of oedema, absent in controls, around the central canal, especially in the thoracic region but also in the cervical and lumbar cord. This oedema may involve both anterior and posterior commissural fibres.

Changes in nervous tissue are more pronounced in rabbits exposed to high pressures. Pial hemorrhages occur on the surface of the cortex, and hemorrhage from the tela choroidea, filling the ventricles, has been observed. Hemorrhages have not been seen, however, in either the grey or white matter of the brain.

Spinal-cord haemorrhages [in rabbits] are of the same kind as, but more severe than, [those] in the monkey.

It is conceivable that as a result of these lesions the sympathetic outflow may be interrupted and that sensory defects may occur as a result of oedema and pressure on the commissures.

Stewart, Russel and Cone<sup>20</sup> report on injuries to the central nervous system of a pheasant by blast during an air raid. The blasted pheasant was found 90 feet from the edge of a bomb crater, dazed and parietic after two large bombs had been dropped, but there was no way of determining how near the bird had been to the actual site of the explosion. It was in a catatonic state, and tended to retain any attitude in which it was passively placed. Microscopic examination of the nervous system showed congested capillaries of the forebrain, associated with numerous petechial hemorrhages, which were most numerous in the hypothalamic area. There were also massive hemorrhages in both lungs and numerous small hemorrhages in the heart. The report of Stewart and his co-workers is essentially in harmony with that of Zuckerman for the more serious cases of blast injury, but Zuckerman and Hooker insist that conspicuous symptoms referable to the nervous system may often be found with little recognizable histologic change.

**Concussion.** In previous experiments on concussion, such as the excellent studies of Pilcher,<sup>21</sup> Schaller et al<sup>22</sup> and Scott,<sup>27</sup> measured blows were delivered to an animal whose head was rigidly fixed, since anesthesia was employed, one criteria of concussion, namely, loss of consciousness, could not be appraised. The following clinical experience of Denny Brown<sup>24</sup> suggested that acceleration of the head in space was essential for the concussion syndrome, rather than a blow on the head per se. An automobile mechanic, when his head was solidly on the concrete floor, had the misfortune to have a car fall off the jack, and his head was pinioned against the floor by the car's differential. He suffered a severe compound fracture, but no symptoms of concussion, indeed, immediately after the accident, the man was unaware that he was seriously injured. In this case, there had been no movement of the head, merely a crushing blow. Similar cases have just been reported by Eden and Turner<sup>25</sup>. If, however, the head is struck when unsupported and is thus able to move, symptoms of concussion inevitably develop. Furthermore, if the head, when moving, is brought abruptly to a stop, deceleration occurs and is similarly effective in producing concussion. On the basis of this reasoning Denny Brown and Russell<sup>24</sup> devised a series of experiments in which a fixed head was struck with a pendulum moving

at velocities between 10 and 30 feet per second, the results being compared with those obtained with similar blows when the head was free to move. With the head fixed, blows that gave severe contusion and fractures of the skull failed to cause concussion. With the free head, three categories of symptoms developed, depending on the intensity of the blow, and usually appeared in the following sequence: shock, concussion and contusion.

**Shock.** When the blow is delivered at about 23 to 24 feet per second, the animal develops the classic symptoms of traumatic shock. The pulse rate slows for a time and then increases, the blood pressure falls, respirations become quick and shallow, and the animal becomes incapacitated for a period of several hours; but the knee jerks and the pinnal and corneal reflexes are unaffected. It is highly significant, especially in view of Hooker's<sup>16</sup> and Zuckerman's<sup>18, 19</sup> work on blast, that a blow on the head can of itself induce symptoms of generalized shock.

**Concussion.** A distinction is made between shock, as such, and symptoms of concussion, which develop when slightly heavier blows are delivered, that is, those struck at a velocity of 25 to 28 feet per second. Following these heavier blows, the corneal and pinnal reflexes are abolished for varying intervals, the resting posture (tonus) of the extensors disappears, and spinal reflexes may be altered or even temporarily abolished. A blow of this magnitude, if delivered to a conscious animal, renders it unconscious, whereas the blow causing shock does not necessarily cause unconsciousness.

The pathologic changes in the brain associated with shock and concussion blows have been carefully sought and have been proved wholly absent so far as ordinary microscopic examination is concerned. There are no petechial hemorrhages and no contused hemorrhagic areas in the medulla or cerebral hemispheres. The microscopic causes of the symptoms of concussion are still obscure, but no doubt they involve some basic intracellular disorganization of the neuron.

**Contusion.** When blows are delivered to the head at a rate greater than 28 feet per second, contusions usually develop in which hemorrhages occur beneath the site of the blow (or as a contrecoup at the opposite side of the head), and petechial hemorrhages are prone to develop, especially in the basal nuclei, brain stem and medulla. Age and other factors, however, affect the actual velocity essential for contusion.

The studies of Denny-Brown and Russell thus indicate that conspicuous concussion may be produced in animals without causing clearcut histologic changes. Studies of Hooker<sup>16</sup> and Zuckerman<sup>11</sup> prove that this is also true of blast concussion. Is there anything in common between direct traumatic concussion and blast concussion?

Zuckerman<sup>18, 19</sup> is of the opinion that lung damage is due to the physical impact of the blast wave against the thoracic wall rather than to sudden distention of the lungs by the positive component of the blast wave, or to a suction effect of the negative component of the blast wave. Such changes as occur in the central nervous system are like-

wise thought to be caused by sudden impact. There are obviously two components to be considered in the blast wave: the primary increase in atmospheric pressure to 100 pounds or more per square inch, and the rate of movement of the blast wave itself. Sudden increase of pressure might rupture the tympanic membrane, but from experience of caisson workers it is not likely that the pressure itself would cause concussion any more than a mechanical blow on a fixed head. A wave of moving pressure that gives acceleration of the body by virtue of its impact on the body wall—and hence imparts an acceleration to the body as a whole, including the head—reproduces in a very precise manner the type of acceleration or deceleration known to be essential for the traumatic-concussion syndrome.

Those who are surprised by the apparent lack of histologic change in cases of concussion will be interested to learn that de Gutiérrez-Mahoney,<sup>26</sup> of Nashville, Tennessee, has confirmed the results of Denny-Brown and Russell, finding that when the fixed head is struck there is in fact no detectable histologic change, but that when the head is given an acceleration by a corresponding blow and concussion results, a widespread demyelination of nerve tracts, followed by a transient appearance of fat droplets throughout the cerebral substance, can be detected; outspoken fat embolism may also result. The fat droplets and emboli tend to disappear entirely within three or four hours after the blow, and de Gutiérrez-Mahoney believes this to be the reason why fat embolism has not been previously demonstrated.

Fat embolism has assumed prominence in the present war, and there are many reports in the current literature, especially from England, concerning its incidence. In a group of 115 cases reported by Robb-Smith<sup>27</sup> in February, 1941, death was attributed to embolism in 25 per cent of cases. In a more recent discussion on fat embolism and the brain, Robb-Smith<sup>28</sup> and others who contributed to the discussion suggest that cerebral complications developing secondarily after an accident are due to the fat emboli that have passed through the lungs into the cerebral circulation. These may arise locally in contused tissues, such as a crushed long bone. Usually, the lungs separate out all the fat globules, but occasionally a pulmonary vein is torn so as to permit escape of fat into the systemic circulation. Robb-Smith states: "In systemic fat embolism the symptoms usually develop two to three days after the accident and are characterized first by delirium, which is frequently very violent, alternating with stupor which merges into coma. Localizing signs are usually absent or, if present, are chaotic. Hyperpyrexia is usual and it is not uncommon to find petechial haemorrhages in the skin of the neck, chest and arms, and their presence greatly facilitates diagnosis." He had not encountered cases in which cerebral fat embolism was attributable to direct traumatic concussion of the head.

### Effects of Blast on Man

High-explosive bombs and shells have been used more widely on civilian populations and at sea during World War II than in any previous conflict. When bombs or shells explode in a confined space, as in a building or on a ship, the blast effects are many times intensified. There is thus no more urgent problem connected with the present war than the analysis of blast and its effect on the human body. Despite this, available literature is scant, and research endeavor has been limited to a small group of investigators in England, who took up the problem to help in designing adequate air-raid shelters for protection from blast,<sup>20</sup> as well as from high-velocity fragments. Although this country has for two years been aware of the bombing of cities and shelling of ships on the high seas, nothing has been done toward investigating blast.

From English sources, especially from the reports of Dean, Thomas and Allison,<sup>30</sup> Falla,<sup>31</sup> Hadfield and his co-workers,<sup>32</sup> Hadfield and Christie,<sup>33</sup> Kretschmar,<sup>34</sup> Krohn,<sup>35</sup> Logan<sup>36</sup> and Thomson,<sup>37</sup> it is believed that death from un complicated primary blast in civilian areas is rare, but well authenticated cases have been reported especially in the recent and well-documented account of 17 cases by O'Reilly and Gloyne.<sup>38</sup> Un complicated cases of primary blast may, however, be relatively uncommon, since to be killed by its effects, the person must be very close to the explosion, that is, within 20 or 30 feet (50-kilo bomb). In these circumstances, the chances of being struck by the blast wave alone and not by splinters is somewhat remote. But there have been many thousands of cases in which primary blast and splinter injuries have coexisted. These have been especially common when a direct hit has been made on a crowded air-raid shelter. Similar episodes have occurred at sea,—in the shelling of crowded transports and warships,—and primary blast should therefore always be suspected in any bombing injury.

The histologic findings in man, so far as they have been described, are similar to those in Zuckerman's<sup>18</sup> monkeys subjected to blast waves of 100 pounds per square inch, namely, pulmonary hemorrhages, contusions and lacerations of other thoracic and abdominal viscera, minor changes in the central nervous system, and occasional areas of subpalp hemorrhage.<sup>39</sup> Evidently, as in animals, profound concussion can occur with little in the way of histologic effect.<sup>30</sup> Whether acute cerebral fat embolism exists in such cases has not been determined.<sup>40-42</sup>

### Therapy

It is not possible to discuss the difficult problems of therapy in cases of cerebral and pulmonary

concussion resulting from primary blast, but one general principle is clear. As more is learned about traumatic concussion in civil life, as well as concussion from blast, it becomes obvious that anoxia plays a large role in the total picture. Blood pressure tends to fall as a result of primary shock.<sup>21</sup> The recent German literature<sup>43</sup> on cerebral blood flow following concussion, moreover, indicates that cerebral circulation becomes diminished, and that the pulmonary damage is frequently accompanied by fat embolism. All these circumstances, in my opinion, indicate the need for oxygen therapy, and for measures designed to improve the systemic and especially the cerebral circulation.<sup>44</sup>

### REFERENCES

1. Mott, F. W. The effects of high explosives upon the central nervous system. *Lancet* 1:331-338, 441-449 and 545-553, 1916.
2. Mitchell, S. W. Morehouse, G. R. and Keen, W. W. Jr. *Reflex Paralysis*. Circular No. 6. Surgeon General's Office, March 10, 1864. 17 pp. New Haven Conn. Yale University School of Medicine, 1941.
3. *Cunha's Wounds and Other Injuries of Nerves*. 164 pp. Philadelphia J. B. Lippincott and Co. 1864.
4. Bowly, A. The Bradshaw lecture on wounds in war. *Lancet* 2:1385, 1915.
5. von Ström, A. Die mikrostrukturellen traumatischen Veränderungen des Nervensystems in Lichte der Kriegserfahrungen. *Schweiz. Arch. f. Neurol. u. Psychiat.* 29:127-152, 1932.
6. Myers, C. S. *Shell Shock in France 1914-18. Based on a war diary*. 146 pp. Cambridge University Press, 1940.
7. Roulinovitch, J. Les blessés de guerre sans blessures. *Bull. méd.*, Paris 54:65-67, 1940.
8. Stevenson, W. F. Note on the cause of death due to high explosive shells in un wounded men. *Brit. M. J.* 2:450, 1915.
9. Arnoux, (Cause of death from shell concussion). *Le Journal Paris* July 6, 1915.
10. Pilscher, C. M. Results of projectile action. *History of the Great War Medical Services. Surgery of the War* (Great Britain). 1:36-57, 1922.
11. Bernal, J. D. The physics of air raids. *Nature* 147:594-596, 1941.
12. Zuckerman, S. Experimental study of blast injuries to the lungs. *Lancet* 2:219-224, 1940.
13. Pilscher, C. and Marchand, L. Quelques observations des syndromes commotionnels suivant des affections organiques du système nerveux central. *Rev. Neurol.* 29:798-811, 1916.
14. Marinéscu, G. Lésions commotionnelles expérimentales. *Rev. Neurol.* 32:319-331, 1918.
15. Mauret, A. and Durante, G. Etude expérimentale de syndrome commotionnel. *Presse méd.* 25:478-481, 1917. Contribution à l'étude expérimentale de lésions commotionnelles. *Rev. Neurol.* 32:97-110, 1919.
16. Carver, V. and Dinsley, D. Some biological effects due to high explosives. *Brain* 42:113-129, 1919.
17. Hooker, D. R. Physiological effects of air concussion. *Am. J. Physiol.* 67:219-271, 1924.
18. Guthrie, T. S. and Melzer, S. J. Phenomena following indirect concussion of the skull. *Am. J. Physiol.* 49:120, 1919.
19. Zuckerman, S. Discussion on the problem of blast injury. *Proc. Roy. Soc. Med.* 34:171-188, 1941.
20. Idem. Blast injury to lung. *Brit. M. J.* 1:645, 1941.
21. Stewart, O. W. Fussell, C. K. and Cone, W. V. Injury to the central nervous system by blast observations on a pheasant. *Lancet* 1:172-174, 1941.
22. Pilscher, C. Experimental cerebral trauma: the fluid content of the brain after trauma to the head. *Arch. Surg.* 35:512-527, 1937.
23. Schaller, W. F., Tamaki, K., and Newman, H. W. Pericerebral hemorrhages of brain experimentally produced in rats by concussion. *Arch. Neurol. and Psychiat.* 45:1-23, 1941.
24. Scott, W. W. Physiology of concussion. *Arch. Neurol. and Psychiat.* 43:270-283, 1940.
25. Denny-Brown, D. and Russell, W. R. Experimental cerebral concussion. *J. Physiol.* 99:153-180. Experimental cerebral concussion. *Brain* 64:93-164, 1941. Knock on the head. *Proc. Roy. Soc. Med.* 34:685, 1941. Denny-Brown, D. Delayed collapse after head injury. *Lancet* 1:371-375, 1941.
26. Eden, K. and Turner, J. W. A. Loss of consciousness in different types of head injury. *Proc. Roy. Soc. Med.* 34:685-691, 1941.
27. de Guiterrez Mahoney, W. The pathogenesis of traumatic unconsciousness: importance of fat embolism. *War Med.* 1:916-917, 1941.
28. Robinson, A. H. T. Pulmonary fat embolism. *Lancet* 1:135-141, 1941.
29. Idem. Discussion on fat embolism and the brain. *Proc. Roy. Soc. Med.* 34:693-694, 1941.
30. Barcroft, J. *Sectional Steel Shelters. Report upon investigation of the standard of protection afforded*. London: His Majesty's Stationery Office, 1939.
31. Dean, D. W., Thomas, A. R. and Allison, R. S. Effects of high explosive blast on the lungs. *Lancet* 2:774-776, 1940.

- 31 Fallis, S. T. Effect of explosion blast on the lungs: report of a case. *Brit M J* 2:255, 1940.
- 32 Hadfield, G., Ross, J. M., Swain, R. H. A., Drury White, J. M., and Jordan, A. Blast from high explosive: preliminary report on ten fatal cases, with a note on the identification and estimation of carboxyhaemoglobin in formal fixed material. *Lancet* 2:478-481, 1940.
- 33 Hadfield, G., and Christie, R. V. Case of pulmonary concussion ("blast") due to high explosive. *Brit M J* 1:77-78, 1941.
- 34 Kretschmar, C. H. Wounds of the chest treated by artificial pneumothorax. *Lancet* 1:832-834, 1940.
- 35 Krohn, P. L. Blast injury to lung. *Brit M. J* 1:645, 1941.
- 36 Logan, D. D. Detonation of high explosive in shell and bomb, and its effects. *Brit M J* 2:864-866, 1939.
- 37 Thomson, F. G. Notes on penetrating chest wounds. *Brit M J* 1:44-46 and 317, 1940.
- 38 O'Reilly, J. N., and Gloyne, S. R. Blast injury of the lungs. *Lancet* 2:423-428, 1941.
- 39 Fulton, J. F. Weir Mitchell Lecture: Neurology and war. *Tr & Stud., Coll. Physicians, Phila.* 8:157-165, 1940.
- 40 Rehwald, E. Neurologisches Übersichtsreferat: Commotio und Contusio cerebri. *Med. Klin.* 36:867-869, 1940.
- 41 McWhibben, P. S. A note on intravascular fat in relation to the experimental study of fat embolism in "shell shock." *Am J Physiol.* 48:331-339, 1919.
- 42 Rowlands, R. A., and Wakeley, C. P. G. Fat embolism. *Lancet* 1:502-507, 1941.
- 43 Wanke, R. Zum Kreislaufgeschehen nach Hirnverletzung (Hirnverletzungsschock). *Arch f. klin. Chir.* 200:189-201, 1940.
- 44 Davis, H. A. Physiologic effects of high concentrations of oxygen in experimental secondary shock. *Arch Surg.* 43:1-13, 1941.

## ENTEROCOCCAL ENDOCARDITIS\*

### Report of Two Cases

DAVID SKINNER, M.D.,† AND JESSE E. EDWARDS, M.D.‡

BOSTON

OF the various bacteria causing subacute bacterial endocarditis, the enterococcus is encountered infrequently. Since we have recently had the opportunity of observing 2 patients with enterococcal endocarditis, it is of interest to review each case and the literature, with particular reference to the pathology and bacteriology.

Thirty-seven cases of enterococcal endocarditis have been reported with varying degrees of completeness in the accessible literature,<sup>1-28</sup> and mention has been made of several more.<sup>6, 29-40</sup>

The clinical course of these cases is not pathognomonic of their etiology; it is indistinguishable from that of the common subacute bacterial endocarditis due to *Streptococcus viridans*. From the blood stream of each of the 37 patients discussed, enterococci were recovered on one or more occasions. The shortest known duration of one of these cases was six weeks, the longest thirteen months, and that of half the cases was between two and three months. Of the 25 patients whose underlying cardiac lesions were given on the basis of clinical or anatomic evidence, 20 had rheumatic, 4 had arteriosclerotic, and 1 had syphilitic valvular disease.

Autopsies were performed on 17 of these 37 patients. In all autopsied cases the clinical diagnosis of subacute bacterial endocarditis was substantiated. In general, the additional findings were the usual ones of multiple embolic phenomena. Five patients had cardiac lesions of special interest. Four had severe myocardial damage characterized by replacement of the muscle fibers by scar tissue.<sup>3, 20, 23</sup> The coronary artery of 1 of these 4 cases was involved in a mycotic aneurysm.<sup>20</sup> In

the fifth patient, there was a small abscess in the myocardium.<sup>16</sup>

In 9 of the 17 cases in which autopsies were performed, an attempt was made to isolate the organism; in each, an enterococcus was cultured from the heart's blood or vegetations, or both. Smears or sections of the heart valves in 3 other cases disclosed gram-positive cocci in pairs and short chains. Enterococci were also recovered in cultures of various embolic abscesses in 5 of the cases.

The portal of entry of the infection was not discussed in 15 of the 37 cases. In 8, it could not be determined. The possible or probable portal of entry stated for the remainder was an infected finger in 1,<sup>2</sup> infected tonsils in 1,<sup>21</sup> the gall bladder in 2,<sup>16, 26</sup> the urinary tract in 2,<sup>8, 9</sup> septic abortion in 3,<sup>10, 17, 20</sup> and the gastrointestinal tract in five.<sup>7, 11, 13, 15, 19</sup> Each of the 2 patients in whom the portal of entry was the urinary tract had a proved enterococcal urinary-tract infection and a urethral stricture. Subsequent to surgical relief of the stricture, each patient developed enterococcal endocarditis. From the gall bladder of 1 of the 2 patients whose portal of entry was considered to be the biliary tract, enterococci were cultured at autopsy. Four of the 5 patients whose gastrointestinal tracts were involved had had acute gastroenteritis. In the fifth patient, autopsy disclosed ulcerations of the rectosigmoid. No bacteriologic studies of the possible portals of entry of the remaining cases were made.

Unfortunately, the characteristics of the organisms recovered were described in detail in so few cases that a comparison of the different strains is not possible. The antigenic properties of only one of the organisms were investigated.<sup>28</sup> It should be noted, however, that half the cases were re-

\*From the Mallory Institute of Pathology, Boston City Hospital.

†Formerly, resident in bacteriology, Mallory Institute of Pathology, Boston City Hospital.

‡Formerly, first assistant in pathology, Mallory Institute of Pathology, Boston City Hospital.

ported prior to the publication of Lancefield's<sup>41</sup> methods of classification

### CASE REPORTS

**CASE 1** A 72-year-old businessman presented himself on March 30, 1939, with the chief complaint of twice having passed blood at the end of urination.

The past history, which revealed that in 1915 he was refused life insurance because of a heart murmur, was otherwise noncontributory.

The patient was first seen in January, 1934, because

obese abdomen. On rectal examination, the prostate was greatly enlarged but soft. There were old blood and smegma about the corona and a moderate balanitis. His physical condition otherwise was essentially normal, not having changed appreciably during the 5-year interval.

Laboratory examinations disclosed a hemoglobin level of 100 per cent and a red-cell count of 5,250,000. A catheter specimen of urine was essentially normal. The blood nonprotein nitrogen level was 46 mg per 100 cc. An intravenous pyelogram showed normal function in each kidney and a large intravesicular prostate, with ele

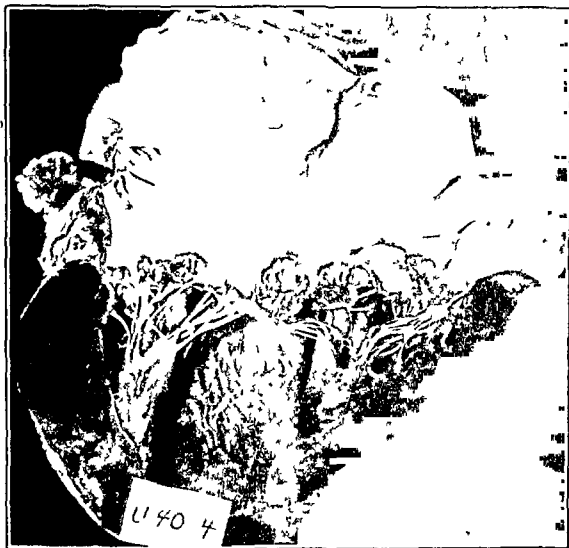


FIGURE 1

*Photograph of the mitral valve in Case 1, showing the fairly large, irregularly deposited vegetations of bacterial endocarditis.*

he suffered a burning sensation in the rectum after defecation. There were no associated urinary symptoms. About 6 weeks later, he began to have a slight burning on urination and to feel uncomfortable. There was diurnal frequency of five or six times and no nocturia. Physical examination revealed a slight, apical, systolic, cardiac murmur, a blood pressure of 200/90, and a moderately enlarged but soft prostate. Proctoscopy yielded negative results. Laboratory data disclosed an essentially normal urine and peripheral blood, a negative Wassermann reaction, and blood sugar and nonprotein nitrogen levels within normal limits. Roentgenographic studies of the chest, gall bladder, gastrointestinal tract and kidneys were essentially negative.

Five years later, in March, 1939, the patient returned with the chief complaint of having twice passed approximately a tablespoonful of blood at the end of urinating clear, nonbloody urine. There was no associated pain or dysuria. The urinary stream had become somewhat smaller during the intervening 5 years.

Physical examination showed that the patient had gained considerably in weight and had developed a very

vation of the ureteral orifices, and back pressure into the ureters.

On April 6, a bilateral vasotomy and a one-stage suprapubic prostatectomy were performed under spinal anesthesia. A very large, vascular prostate was enucleated by the usual technique. The bladder wall was greatly hypertrophied, and the histologic appearance of the prostate was that of benign enlargement. The patient had an uneventful convalescence.

Two months after the operation, in June, the patient began to exhibit an evening temperature of 100 to 102°F. Throughout the rest of the day, he felt well and at no time had chills. There occurred an occasional slight swelling of the right ankle, which was considered to be due to a mild pelvic phlebitis. However, the fever persisted, and, early in July, a blood culture grew an organism that morphologically resembled a pneumococcus.

The patient was again hospitalized. He had no complaints except the evening fever. His general physical condition was essentially as before. The prostatectomy wound was well healed, and the blood pressure was 140/80. Urinalyses showed only an occasional leukocyte



in the sediment. The hemoglobin level was 70 per cent, the red-cell count 3,000,000, and the white-cell count 14,000. The blood nonprotein nitrogen level was within normal limits. A roentgenogram of the chest taken with a portable machine showed a prominent heart shadow but otherwise was not remarkable. A blood culture taken on July 19 grew organisms that were similar in appearance to those previously recovered and were identified as enterococci. Three carious teeth were extracted. From their roots, the same organisms were cultured. Sulfapyridine was given empirically until a blood level of 11.5 mg. per 100 cc. was obtained. Because there was no amelioration of the fever and because the blood nonprotein nitrogen level reached 60 mg. 100 cc., the drug was withheld.

The patient was allowed to go home, where he continued to exhibit an evening temperature of 100 to 102°F. He gradually failed. On December 20, the blood hemoglobin, erythrocyte and leukocyte levels were within normal limits. Blood cultures taken on December 28 again grew enterococci. The patient died on January 4, 1940.

**Autopsy.** An autopsy was performed 12 hours post mortem. Only the pertinent findings are given.

The heart was of normal size, weighing 400 gm. The myocardium was firm and yellowish to deep red. In the lateral wall of the left ventricle approximately 2 cm. from the apex was a focus 1 cm. in diameter in which the myocardium was distinctly yellow. The foramen ovale, measuring 3 mm. in diameter, was anatomically though not functionally patent.

The mitral, aortic and tricuspid valves were the sites of a bacterial endocarditis, the lesions being much more extensive on the mitral than on the other valves (Fig. 1). On the mitral valve, the vegetations, measuring 5 mm. in thickness, were attached to the auricular surface of each cusp and extended slightly along the adjacent chordae tendineae. The surfaces of the vegetations were irregular, and their color varied from yellowish brown to gray. Although friable, they showed foci of calcification, especially in their basal portions. On and near the corpora arantii of the aortic valve were small, gray, friable vegetations, the aggregate measurement of those on each cusp being 4 by 3 by 2 mm. Along the line of closure of the tricuspid cusps was a row of noncontinuous, shallow ulcers measuring up to 8 mm. in diameter. Their bases were yellow and firm, suggesting calcification. The pulmonary valve was normal. None of the valves showed any evidence of disease preceding the bacterial endocarditis.

The aorta showed a moderate degree of atherosclerosis, with focal ulceration in the abdominal portion. In the right common and external iliac veins were small mural thrombi that appeared organized. These lesions were brownish-gray nodules measuring 4 mm. in diameter and did not appreciably narrow the lumens.

The spleen was moderately enlarged, weighing 500 gm. The capsular surface was smooth, glistening and purple except at one point situated at the junction of the diaphragmatic and gastric surfaces. Here was a depression measuring 1.0 by 0.8 by 0.5 cm. The tissues directly beneath this area for a depth of 5 mm. were firm and grayish yellow. Elsewhere, the cut surfaces were deep reddish purple and were studded with numerous bulging, translucent, semigelatinous nodules measuring up to 1 mm. in diameter.

The kidneys were of normal size, their combined weight being 300 gm. The capsules stripped with ease and revealed pale-gray, smooth surfaces on which were numerous linear and punctate red areas suggesting hemor-

rhages. Each cortex measured 5 mm. in thickness. On the pale-gray cut surfaces were punctate red areas.

The prostatic urethra was wide, measuring 1 cm. in diameter. It was walled by firm, fibrous prostatic tissue, which averaged 1 cm. in thickness and from which several gray nodules bulged above the cut surface. The seminal vesicles were slightly pale and thicker than usual.

The rectum contained a polyp measuring 1.0 by 0.8 by 0.5 cm.

Microscopic examination of the various tissues substantiated the anatomic findings. A section of the left ventricle taken through the yellow areas, revealed scattered, small areas in which the muscle fibers had lost their nuclei and had developed a granular cytoplasm. In some places a small number of muscle fibers had disappeared, only stroma with dilated capillaries remaining.

The bacterial endocarditis appeared to be of longest duration on the mitral valve. A section of the cusp showed it to be thickened by fibrous tissue, infiltrated with lymphocytes, plasma cells and macrophages, and to have capillaries coursing through breaks in the elastica. On the auricular surface of the valve were several clumps of gram-positive diplococci partially covered with fibrin

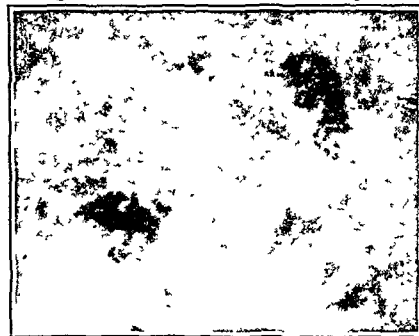


FIGURE 2.

*Photograph of the mitral vegetation in Case 1. Gram-positive cocci are present in clusters and suggestive chains (Gram-Weigert stain,  $\times 1350$ ).*

(Fig. 2). In the underlying endocardium was young granulation tissue heavily infiltrated with neutrophilic leukocytes.

The section of the aortic valve showed a more recent and more acute lesion. Here was an ulceration extending through the entire thickness of the leaflet. At the margin of the ulcer were clumps of bacteria and organizing fibrin infiltrated with polymorphonuclear leukocytes. The fibrous thickening and vascularity seen in the mitral valve were absent.

The Malpighian corpuscles of the spleen contained a moderate amount of amyloid. Beneath the depression in the splenic capsule, the parenchyma was replaced by fibrous tissue infiltrated with a moderate number of lymphocytes, plasma cells and macrophages.

In the kidney, numerous glomerular spaces and adjacent tubular lumens contained fresh and old blood. There was no definite glomerular necrosis. The basement membranes of many glomerular tufts were thickened by a slight to moderate amount of amyloid.

The prostatic tissue showed moderate fibrosis but no evidence of active inflammation. However, the mucosa of the seminal vesicles was thickened by granulation tissue and contained small numbers of gram-positive diplococci. Within the lumens of the vesicles were polymor-

phon clear leukocytes, lymphocytes and macrophages

The rectal polyp was a typical benign polyp. At its base was an infiltration of a small number of neutrophilic leukocytes.

The final diagnoses were subacute bacterial endocarditis, with extensive involvement of the mitral valve and slight involvement of the aortic and tricuspid valves, focal myocardial infarction, amyloidosis of the spleen, kidney and adrenal glands, healed infarct of the spleen, polyp of the rectum, old thrombophlebitis of the right common and external iliac veins, chronic seminal vesiculitis.

**CASE 2.** A 60-year-old, Russian Jewish printer was admitted to the hospital on July 12, 1939, with the chief complaint of difficulty in breathing, cough and intermittent pain in the chest increasing in severity during the preceding 4 weeks.

The past history was noncontributory.

In 1933, the patient first noted slight difficulty in breathing. Despite gradually increasing shortness of breath he was able to continue work until March, 1936, when he was admitted to the hospital with the chief complaints of difficulty in breathing when prone and of swelling of the legs.

Physical examination at that time revealed a well developed and well nourished man experiencing slight dyspnea. Moist rales were heard in the posterior, basal portion of each lung field. The heart was enlarged to the left, and the heart sounds were of fair quality, without murmurs. The pulse was irregular, with a rate of 120. The blood pressure was 160/110. The lower border of the liver was palpated three fingerbreadths below the right costal margin in the right midclavicular line. Varicosities and marked pitting edema were present in both lower legs.

Laboratory data revealed a hemoglobin level of 85 per cent (Sahli), and a white-cell count of 5800. The blood nonprotein nitrogen level was 27 mg per 100 cc. A blood Kahn reaction was negative. The urine was essentially normal. An electrocardiogram disclosed a ventricular rate of 85 and a QRS interval of 0.08 second,  $T_1$  was upright,  $T_2$  diphasic, and  $T_3$  flat, and the axis was normal. These findings were interpreted as indicating auricular fibrillation and myocardial damage.

The patient responded favorably to the administration of digitalis and was discharged on the 13th hospital day. Thereafter, he continued to take digitalis and was able to work intermittently for about 2 years. During 1938, he found it necessary to restrict his activity because of progressive difficulty in breathing on exertion. About 3 months before his final admission to the hospital, he developed moderate difficulty in breathing when at rest, a moist, unproductive cough, with associated pain in the chest, intermittent swelling of the ankles and episodes characterized by hot and chilly sensations. For the week preceding entry, he felt especially "choked up."

Physical examination in July, 1939, revealed the patient to be orthopneic, cyanotic and in obvious respiratory distress, with a moist cough. The tongue was dry, and the teeth moderately carious. The pupils were irregular and slightly dilated, and reacted sluggishly to light. Ophthalmoscopic examination disclosed moderate tortuosity of the arteries and moderate venous congestion, with moderate arteriovenous nicking. There were bilateral pulsations at the root of the neck and moderate distention of the cervical veins. There were dullness, diminished breath sounds and rales at the bases of both lungs, and there was an area of dullness, with loud bronchial breathing and bronchophony, at the angle of the left scapula. The point

of maximum cardiac impulse was at the left anterior axillary line in the 6th interspace, and the area of supra-cardiac dullness was increased in width. At the apex was a systolic thrill. A harsh, high pitched systolic murmur was heard over the entire precordium and was loudest at the apex. There was a soft, blowing diastolic murmur at the mitral area and the right sternal angle, but it was loudest over the sternum. The pulmonary second sound was louder than the aortic. The cardiac rhythm was totally irregular, and the ventricular rate averaged 70. The blood pressure was 170/65. There was a right inguinal hernia. The area of hepatic dullness extended three fingerbreadths below the costal margin in the right midclavicular line. Rectal examination showed external hemorrhoids. There was moderate pitting edema of the lower legs. A vascular tumor was present on the right palm. The radial and brachial arteries were moderately thickened and tortuous. The reflexes were physiologic.

Laboratory data showed the urine to be acid and to have a specific gravity varying from 1.011 to 1.020. Albumin and sugar were constantly absent. The urinary sediment contained 0 to 5 leukocytes and 0 to 3 granular casts per high power field. Hematologic studies showed a red cell count of 4,100,000, a hemoglobin of 83 per cent (Sahli) and white-cell counts varying from 31,600 to 57,000. Differential leukocyte counts averaged 88 per cent neutrophils, 8 per cent monocytes and 4 per cent lymphocytes. A blood Hinton reaction was negative. Nonprotein nitrogen levels of 86 and 89 mg per 100 cc were obtained. Roentgenograms of the chest showed a general enlargement of the heart without increase in the size of the aorta, congestive changes in both lower lobes and a pneumonic process in both midlung fields. An electrocardiogram taken the day after admission disclosed auricular fibrillation, a ventricular rate of 95, a QRS interval of 0.07 second,  $T_1$ ,  $T_2$  and  $T_4$  diphasic with low origin,  $T_3$  inverted with low origin, and a normal axis. The interpretation was auricular fibrillation and myocardial damage. On the same day, the vital capacity was 2.2 liters, the circulation time 23 seconds, and the venous pressure in the left arm 7 cm of water. A sputum culture grew a streptococcus with alpha hemolysis and *Staphylococcus aureus*. Seven daily blood cultures grew enterococci.

The patient's temperature rose to 101.1°F on the 2nd day, dropped to normal for 4 days, and terminally rose to 100.1°F. The pulse rate averaged 88, except for a rise to 120 during the last 2 days. Similarly, the respiratory rate averaged 30, with a terminal rise to 52. Treatment consisted in venesection, with removal of 600 cc of blood, digitalis, Mercupurine, aminophyllin and sulfapyridine. During the 2nd day, the patient developed a Cheyne-Stokes type of respiration, which continued intermittently thereafter. The cardiac sounds varied from a harsh, high pitched, apical systolic murmur and a soft, blowing diastolic murmur to low pitched, booming systolic and low pitched diastolic murmurs. On several occasions, the diastolic murmurs were inaudible, and once a soft aortic diastolic murmur was heard. On the 3rd hospital day, petechiae were noted in the right conjunctiva and over the right upper arm. The patient failed to improve, developing on the 7th day a persistent Cheyne-Stokes type of respiration, increasing temperature and pulse rate, and rales. He died on the following day, July 20.

**Autopsy.** An autopsy was performed 12 hours post mortem. Only the important findings are given.

The heart was increased in size, weighing 500 gm. The myocardium of each ventricle was hypertrophied, the left measuring 2 cm in thickness, and the right 8 mm. The coronary arteries showed a mild degree of athero-

sclerosis but no appreciable degree of narrowing of their lumens.

The mitral valve evinced a well-established rheumatic stenosis, the valve orifice being narrowed to a diameter of approximately 1 cm. On the auricular surfaces of the fused mitral cusps was a bulky vegetation. This was firmly attached to the endocardium and measured 2.3 cm. in width and 6 mm. in height. The remaining valves were normal.

In the cecum was a smooth-surfaced polyp measuring 8 mm. in diameter. Adjacent to this was an area of superficial ulceration with a dark, brownish-green base, measuring 4 cm. in greatest extent. The rectum showed some hemorrhoids.

The kidneys were reduced in size, their combined weight being 190 gm. The capsules stripped with ease, and the parenchymal surface was smooth except for an occasional linear scar 3 mm. or less in depth. On section, the cortex averaged 5 mm. in thickness and was pinkish red, with no evident hemorrhages.

Microscopic examination of the various tissues substantiated the anatomic findings. A section of the left ventricle revealed small foci in which the muscle fibers had disappeared; only stroma with dilated capillaries and scattered pigment-laden macrophages remained.

A section of the mitral valve disclosed an ulceration extending through the entire substance of the leaflet. The hiatus was filled by a vegetation composed of partially organized, old fibrin, erythrocytes, leukocytes and gram-

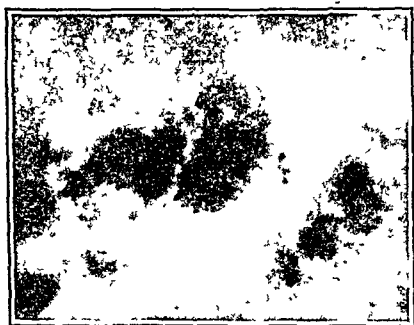


FIGURE 3.

Photograph of the mitral vegetation in Case 2. Gram-positive cocci are present in clusters (Gram-Weigert stain,  $\times 1350$ ).

positive cocci in pairs, short chains and clusters (Fig. 3). Beneath the ulcerated surfaces was young granulation tissue. In the substance of the leaflet remote from the ulceration were foci of necrosis and infiltration of moderate numbers of polymorphonuclear leukocytes.

In the gastrointestinal tract were two lesions, one in the rectum, and one in the cecum. The section of the rectal lesion disclosed hemorrhoids of moderate size and also an acute inflammatory process in the mucosa. The lesion in the cecum was characterized by infarctlike necrosis, with ulceration and infiltration and a moderate number of neutrophils and many diplococci and bacilli. Cocci in pairs and short chains were the predominating organisms in the cecal wall.

The final diagnoses were: subacute bacterial endocarditis involving the mitral valve; old rheumatic heart disease, with mitral stenosis; myocardial hypertrophy; focal myocardial infarction; pulmonary congestion and edema; polyp and focal acute ulceration of the cecum; hemorrhoids.

## BACTERIOLOGY

The organism of Case 1 (Strain A) was obtained in pure culture from four ante-mortem cultures, in conjunction with a *Str. viridans* from an extracted tooth, in pure culture from the heart's blood at autopsy, and in conjunction with a *Staph. albus* from the vegetation. The organism of Case 2 (Strain O) closely resembled that of Case 1. This strain was obtained in pure culture from six ante-mortem blood cultures and from another in conjunction with a *Staph. albus*. The post-mortem blood culture was negative. Cultures of the vegetation and an unorganized mural thrombus yielded the organism in pure culture.

On smear, the organisms are gram-positive, lanceolate diplococci, often appearing encapsulated, and arranged singly and in short chains. They grow well in broth, producing an even turbidity. On the surface of a blood-agar plate (20 per cent defibrinated sheep blood), they form discrete, small, grayish-white convex colonies, which produce a very faint zone of alpha hemolysis that is best seen after a colony is scraped aside. The organisms grow readily on the surface of 40 per cent bile agar and are insoluble in bile. They produce acid fermentation of dextrose, lactose, galactose, maltose, trehalose, salicin, sorbitol and mannitol, and split esculin. They do not ferment sucrose, arabinose, raffinose or inulin. The pH of dextrose broth is lowered from 7.0 to 4.3. Acid and a slight clot are formed in litmus milk. The two strains differ somewhat in their resistance to heat: Strain A resists a temperature of 60°C. for thirty minutes, whereas Strain O resists that temperature for ten minutes. Extracts of the organisms were tested for precipitin reactions with serums of Lancefield's Groups A to H streptococci, inclusive, and gave reactions with Group D anti-serums. These two strains were found not to correspond with the few known serologic types within this group.

## DISCUSSION

The term "enterococcus" is best used to denote a group of related organisms whose normal habitat is the intestinal tract. The enterococcus is described as a gram-positive, lanceolate diplococcus occurring in short chains.<sup>29, 42-47</sup> It is often somewhat pleomorphic and sometimes appears encapsulated. On the surface of blood agar, it grows well as a round, convex, lenticular, sharply contoured colony producing a slight amount of alpha hemolysis. It also grows well in broth or on agar containing 10 per cent, 20 per cent or 40 per cent bile, and is insoluble in bile. The organism is hardy, requiring infrequent transplanting, and

most strains resist a temperature of 60°C. for thirty minutes. Its biochemical activities include the formation of acid and a soft clot in litmus or methylene blue milk and the reduction of the pH of dextrose broth from 7.5 to 4.2. Acid without gas is produced in dextrose, lactose, sucrose, trehalose, salicin, mannitol and sorbitol, and inulin and raffinose are not fermented. Esculin is split. Antigenically, this group comprises Group D of Lancefield's classification.<sup>37, 41, 46, 47</sup>

Attempts at subdivision of the group on the basis of cultural and biochemical characteristics have resulted in considerable confusion. The American and English authors, exemplified by Sherman,<sup>46</sup> subdivide the enterococcus group into four closely related species, *Str. faecalis*, *Str. liquefaciens*, *Str. zymogenes* and *Str. durans*, of which the first is the type form. The more recent German authors, exemplified by Gundel,<sup>48</sup> divide the enterococci into Types A and B, of which Type B corresponds to the typical enterococcus and Type A exhibits less vigorous cultural and biochemical activities and less pathogenicity for mice than Type B. The development by Lancefield<sup>41</sup> of a practicable method of grouping streptococci on the basis of antigenic structure has already shown that many of the various species of enterococci belong to Group D.<sup>47</sup>

Comparison of the characteristics of the organisms recovered from these 2 cases with those of the type organism showed a striking similarity. In the tests used, Strain A reproduced the type reaction except for its failure to ferment sucrose. Similarly, Strain O differed from the type organism only in its failure to ferment sucrose and in its heat resistance. Despite these aberrations, it seems evident on the basis of cultural, biochemical and antigenic properties that these two organisms are enterococci.

Comment should also be made concerning the possible sources of entry of the enterococcus into the blood stream in these 2 cases. In Case 1, autopsy revealed two possible sources, the infected polyp of the colon and the seminal vesicles. The inflammatory lesion in the polyp was not extensive and undoubtedly originated at a later date than the endocarditis. On the other hand, the seminal vesicles evinced a long-standing inflammatory process and contained organisms morphologically similar to the enterococcus. These observations, together with the clinical history of the development of the endocarditis subsequent to the prostatectomy, imply but do not prove that the seminal vesiculitis was the portal of entry of the enterococcus. In Case 2, there were in the cecum and rectum moderately acute ulcerations heavily infiltrated with bacteria morphologically similar

to enterococci. Although these ulcerations might constitute the portal of entry of the organism, the acuteness of the lesions probably indicates that they were of more recent origin than the endocarditis.

Two other observations deserve mention. In each case, throughout the myocardium, were focal areas in which the muscle fibers had disappeared, only the stroma remaining. Such lesions are consistent with those produced by arterial occlusion. Although no occlusions of the coronary arteries were demonstrated, it is reasonable to assume that some of the smaller branches of the arteries were obstructed, possibly by emboli.

The other and more unusual complication of bacterial endocarditis was amyloidosis. Deposits of amyloid were found in the spleen, adrenal gland and kidney in Case 1. An explanation of its occurrence here might lie in the long duration of the endocarditis.

#### SUMMARY

Two cases of subacute bacterial endocarditis caused by an enterococcus are presented.

In Case 1, the symptoms of endocarditis appeared following a prostatectomy. The patient died seven months later. Necropsy showed typical vegetations involving the mitral, aortic and tricuspid valves, focal myocardial infarction, evidence of seminal vesiculitis of long duration and the unusual finding of amyloidosis. The organism (Strain A) was recovered from four ante-mortem blood cultures and an extracted tooth, and from the heart's blood and the vegetations at autopsy. There was no demonstrable underlying cardiac disease. The portal of entry may have been the infected seminal vesicles.

In Case 2, the symptoms of endocarditis appeared in a patient who had cardiac decompensation, which had progressed slowly throughout a six-year period. The duration of the endocarditis was probably about three months. Necropsy evinced old rheumatic heart disease, with involvement of the mitral valve, typical vegetations on that valve and focal myocardial infarction. Although fairly acute ulcerations of the rectum and sigmoid were found, these probably were of too recent occurrence to have been the portal of entry. The organism (Strain O) was recovered from seven ante-mortem blood cultures and from the vegetations and an unorganized mural thrombus at autopsy.

The characteristics of these organisms are those of an enterococcus, with the exceptions of the failure of both strains to ferment sucrose and the diminution of the heat resistance of Strain O. Both

strains are members of Group D (enterococcus) of Lancefield's classification of streptococci.

We are greatly indebted to Dr. A. R. Kimpton for permission to report Case 1 and to Dr. R. C. Lancefield for grouping and attempting to type the organisms.

## REFERENCES

1. MacCillum, W. G., and Hastings, T. W. A case of acute endocarditis caused by *Micrococcus zymogenes* (nov. spec.), with a description of the microorganism. *J. Exper. Med.* 4:521-534, 1899.
2. Braxton Hicks, J. A. An unusual organism (*Micrococcus zymogenes*) in a case of malignant endocarditis. *Proc. Roy. Soc. Med.* 5: (path. sect.) 126-130, 1912.
3. Costa, S., and Boyer, L. Sur un microcoque isolé du sang, d'un épanchement articulaire et d'un nodule sous cutané au cours d'une endocardite infectieuse maligne à forme prolongée. *Compt. rend. Soc. de biol.* 88:188-190, 1923.
4. Costa, S., and Boyer, L. Sur un microcoque isolé du sang au cours d'un deuxième cas d'endocardite infectieuse à forme prolongée. *Compt. rend. Soc. de biol.* 88:493, 1923.
5. Gallavardin, L., and Langeron, L. Endocardite infectieuse à entérocoque. *Lyon méd.* 132:314-317, 1923.
6. Gundel, M., and Seeber, F. Die klinische Bedeutung der Enterokokken in Magen-Darmkanal. *Deutsches Arch. f. klin. Med.* 164:190-201, 1929.
7. Rouslacroix, A., Zuccoli, and Martin, P. Endocardite maligne et septicémie à entérocoques. *Compt. rend. Soc. de biol.* 95:499-502, 1926.
8. Meyer, K. Über Enterokokkensepsis. *Klin. Wchnschr.* 6:2045-2047, 1927.
9. Fuss, E. M. Urogene Enterokokkensepsis. *Med. Klin.* 23:245, 1927.
10. Tidow, G. Enterokokkensepsis unter dem Bilde der Endocarditis lenta. *Med. Klin.* 25:872, 1929.
11. Duvernay and Gerbay. Entérocoque Myocardite Mort. *Lyon méd.* 143:636-638, 1929.
12. Cade, A. Septicémie à entérocoques avec endocarditis à marche lente. *Lyon méd.* 143:689-691, 1929.
13. Gundel, M. Bakteriologie und Klinik seltener Streptokokkeninfektionen. *Deutsches Arch. f. klin. Med.* 168:129-155, 1930.
14. Rosenberg, G. Der Enterokokkus als Erreger von Endocarditis chronica. *Zentralbl. f. Bakt.* (Abt. I) 121:75-85, 1931.
15. Boyer, L., and Sauvan, A. Sur un germe du type entérocoque obtenu par hémoculture dans un cas d'endocardite maligne. *Compt. rend. Soc. de biol.* 108:104-106, 1931.
16. Rosenberg, G. Zur Kenntnis der Enterokokken Endokarditiden. *Klin. Wchnschr.* 11:359-362, 1932.
17. Dumas, A., and Jossierand, P. Endocardite infectieuse à entérocoque (Retrécissement mitral antérieur. Evolution rapide après une fausse couche). *Lyon méd.* 151:637-643, 1933.
18. Cossio, P., Berconsky, I., and Fisher, A. Endocarditis infecciosa a enterococcus. *Semana méd.* 2:1911-1914, 1933.
19. Grogler, F. Über Enterokokkenendokarditis. *Zentralbl. f. inn. Med.* 55:689-693, 1934.
20. Wallach, K. Subacute enterococcus endocarditis. *J. Mt. Sinai Hosp.* 1:80-83, 1934.
21. Baum, M. Ein Fall von Enterococcus Endokarditis. *Wien klin. Wchnschr.* 48:1067-1069, 1935.
22. Reiners, H. Enterokokken Endokarditis. *Klin. Wchnschr.* 15:1067-1069, 1936.
23. Grogler, F. Neue Erfahrungen zur Frage der Enterokokkenendokarditis. *Deutsches Arch. f. klin. Med.* 180:153-163, 1937.
24. Waaler, E. Bacterial endocarditis caused by hemolytic fecal streptococci (enterococci). *Acta med. Scandinav.* 91:121-126, 1937.
25. Clements, A. B. Enterococcus endocarditis. *New York State J. Med.* 37:1842-1844, 1937.
26. Otto, E. Beitrag zur Kenntnis der Enterokokkenendokarditis. *Klin. Wchnschr.* 17:1847-1850, 1938.
27. Rohleder, T. Ein Beitrag zur Frage der Enterokokken-Endokarditis. *Monatschr. f. Kinderh.* 73:361-366, 1938.
28. Williams, C. Bacterial endocarditis due to the *Streptococcus faecalis*. report of a case. *Am. Heart J.* 18:753-758, 1939.
29. Andrewes, F. W., and Horder, T. J. A study of the streptococci pathogenic for man. *Lancet* 2:708-713, 775-782 and 852-855, 1906.
30. Marchal, G., and Jaubert, A. Étude bactériologique de l'endocardite infectieuse secondaire lente à streptocoques. *Presse méd.* 34:324-327, 1926.
31. Ribeyro, R. E. Enterococcemia. *Crón. méd., Lima* 44:4-8, 1927.
32. Clerici, A. Endocardite infettiva da enterococco. *Gazz. d. osp.* 49:353-355, 1928.
33. Wyss. Cited by Reiners<sup>22</sup>.
34. Hille, J., Girard and Odinet, J. Cited by Cossio, Berconsky and Fisher<sup>18</sup>.
35. Henske. cited by Reiners<sup>22</sup>.
36. Parenti, G. C. Endocardite da enterococco. *Sperimentale, Arch. di biol.* 88:218-228, 1934.
37. Lancefield, R. C., and Hare, R. The serological differentiation of pathogenic and non pathogenic strains of hemolytic streptococci from parturient women. *J. Exper. Med.* 61:335-349, 1935.
38. Kolar, K. Immunotherapy in enterococcus septicemia and endocarditis. *Bratisl. lekár. listy* 16:561-575, 1936.
39. Picard, J., and Marquet, G. Septicémie entérocoque maligne endocardite, pleurésie séro fibrineuse modes d'action du carbone intra-veineux. *Progres méd.* pp. 862-868, 1936.
40. Duthoit, A., and Demarez, R. Deux cas de septicémie à entérocoques. *Echo méd. du Nord* 8:773-780, 1937.
41. Lancefield, R. C. A serological differentiation of human and other groups of hemolytic streptococci. *J. Exper. Med.* 57:571-595, 1933.
42. Topley, W. W. C., and Wilson, G. S. *The Principles of Bacteriology and Immunity*. Second edition 1645 pp. Baltimore Wm. Wood and Co., 1936. Pp. 453-458 and 468.
43. Dible, J. H. *A System of Bacteriology in Relation to Medicine*. Vol. II. 419 pp. London His Majesty's Stationery Office, 1929. Pp. 124-136.
44. Kolle, W., Kraus, R., and Uhlenhuth, P. Enterococcus. In *Kolle und Wasserman's Handbuch der pathogenen Mikroorganismen*. Third edition Vol. VI. Jena Gustav Fischer, Berlin and Wien Urban und Schwarzenberg, 1929. Pp. 399-402.
45. Dible, J. H. The enterococcus and the faecal streptococci their properties and relations. *J. Path. & Bact.* 24:3-35, 1921.
46. Sherman, J. M. The streptococci. *Bact. Rev.* 1:3-97, 1937.
47. Smith, F. R., and Sherman, J. M. The hemolytic streptococci of human feces. *J. Infect. Dis.* 62:186-189, 1938.
48. Gundel, M. Das biologische System der Streptokokken. *Zentralbl. f. Bakteriologie*. (Abt. I) 115:44-66, 1929.

# LEFT INGUINAL HERNIA WITH ACUTE MECKEL'S DIVERTICULITIS AND PERITONITIS

## Report of a Case

ROLI LIU, MD,\* AND SAMUEL T LADD, MD\*

PORTSMOUTH, NEW HAMPSHIRE

WHEN acute inflammation of Meckel's diverticulum is encountered at operation, it is usually recognized by the surgeon. We wish to report a case in which Meckel's diverticulitis complicated a strangulated left inguinal hernia. The diagnosis was not apparent until the patient had left the hospital and a considerable amount of detective effort had been expended.

## CASE REPORT

A 75 year-old, Irish-born, retired machinist was admitted to the Portsmouth Hospital on February 12, 1941. It was impossible to obtain an accurate detailed history from him because of mental confusion. The first symptom was generalized abdominal pain which began 2 weeks before admission. There had been some retching at the onset, but no vomiting. The patient had not noted any distention of the abdomen, nor did he describe the abdominal pain as crampy. During the 2 weeks before admission, he felt a steady soreness across the abdomen, and was unable to eat. The bowels moved without cathartics about once in three days. The first bowel movement was on the day of admission. There was no blood or mucus in the stools.

For the previous 2 years, the patient had noted gradually developing symptoms of prostatism. His urinary stream had become smaller, there was increasing difficulty in starting the urine, and he had nocturia of two to five times. At no time had he seen blood or pus in the urine. The patient had noted some dyspnea on exertion during the preceding 6 months, but no edema or paroxysmal nocturnal dyspnea. He had some orthopnea and used two pillows at night. The family and marital histories were noncontributory. The patient had used alcohol quite freely until 2 years before admission when he had stopped suddenly at the direction of his physician.

Physical examination showed a well developed and well nourished man with respirations of 30 and signs of dehydration. His pulse was completely irregular, with a radial pulse deficit of 15 beats. There were many coarse rales throughout the lungs, but no area of consolidation was found. The abdomen was soft and not distended, it was tender throughout, the maximum tenderness being over a mass in the left groin. This mass was firm and rounded, measured 4 cm in diameter, and was not reducible. It lay just above the center of Poupart's ligament. The blood pressure was 130/70. There were 4 or 5 white blood cells per high power field in the urine, but no albumin or sugar. The white-cell count was 29,000, with 89 per cent polymorphonuclear leukocytes. The temperature was 102.7° orally.

Four cat units of Digifolin were given intramuscularly, an intravenous injection of 10 per cent glucose in physiological saline was begun, and the operation on the mass in the left lower quadrant was undertaken with local

anesthesia. The preoperative diagnosis was strangulated inguinal hernia with a question of Richter's hernia.

The peritoneum was entered at a point above the hernia, and the sac opened from above. The neck was very narrow and consisted of a thick fibrous band. There was free seropurulent fluid in the abdominal cavity, with large flakes of fibrin. The loops of sigmoid and small intestine were bound together with fine adhesions. The posterior wall of the sac was composed of a 4 cm long, acutely inflamed tip of what appeared to be an appendix and its mesentery (Fig 1). The organ was visualized 4

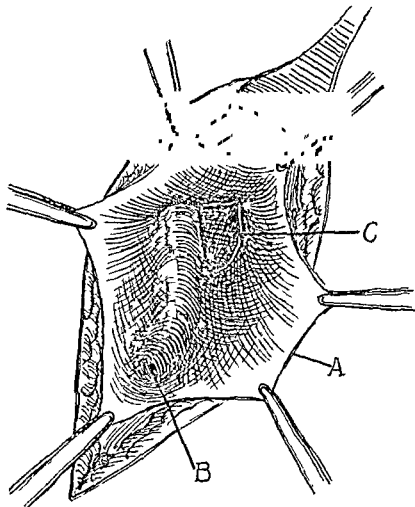


FIGURE 1 Drawing of Operative Findings

A—cut edge of hernial sac, B—acutely inflamed tip of Meckel's diverticulum, C—cut edge of neck

cm above the tip, in the medial direction, and this portion seemed to lie entirely in the retroperitoneal area. Further exposure was not possible without extension of the incision.

In view of the patient's general condition, the simplest procedure was adopted: the inflamed tip was amputated, and the sac removed with it en masse. When the peritoneum was closed, it was necessary to overlap the edges somewhat so as not to incorporate the stump in the suture line.

The hernia was repaired with catgut, the second method of Halsted being used. The cord was left in its bed, the cremaster muscle was imbricated beneath the conjoined tendon and the conjoined tendon beneath the lower leaf of external oblique muscle, with the leaves of the

\*Surgeon Portsmouth Hospital

external oblique muscle overlapped. A drain was left in the lower angle of the wound. The report of Dr. H. N. Kingsford on the specimen was as follows:

The specimen consists of a sac, open at one end. It reveals a projection into its lumen measuring 4 by 1 cm. Sections show a peritoneal covering, subperitoneal tissue and two smooth-muscle layers, with a marked purulent exudate on the lumen edge of the section; there is absolutely no evidence of mucosa. This could be a Meckel's diverticulum or an appendix.

The convalescence was complicated by bronchopneumonia on the 2nd postoperative day; this was controlled by sulfathiazole. On the same day, the patient developed acute urinary retention, which necessitated an in-lying catheter. He was digitalized by the 3rd day, and from then on ran a regular pulse. The gastrointestinal tract revealed its functional integrity soon after operation by the passage of flatus, which continued to occur without abdominal discomfort. Sepsis developed in the wound, but 5 weeks after operation there was only a small sinus and no evidence that the hernia was recurring. The patient had recovered sufficiently 2 weeks after operation to undergo a transurethral resection for benign prostatic hypertrophy.

With the available evidence, it seemed that we had been dealing with an acute appendicitis and peritonitis in a left inguinal hernia. However, a barium enema done postoperatively showed the cecum in the right lower quadrant, with the appendix well outlined for a length of 10 cm. It was freely movable and showed no evidence of attachment to the site of the hernial sac. Previous to prostatectomy, a cystogram gave no indication of a bladder diverticulum. A gastrointestinal series six weeks after operation showed a loop of small bowel, about 30 cm. above the ileocecal valve, close to the anterior abdominal wall in the left

lower quadrant and apparently attached in this position (Fig. 2).

In the last analysis, it seems that the diagnosis was acute Meckel's diverticulitis in a left in-

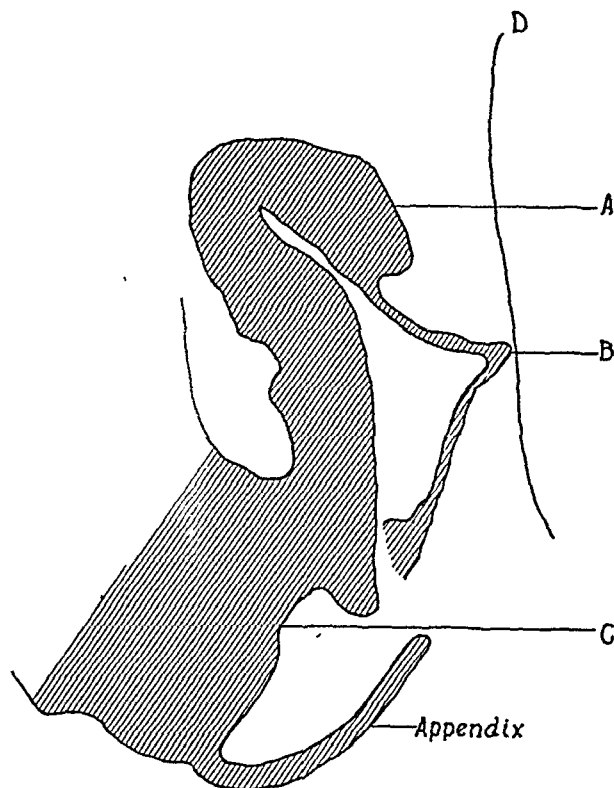


FIGURE 2. Tracing of X-ray Plate Six Hours after a Barium Meal.

A—terminal ileum; B—point of fixation to site of hernial sac; C—cecum; D—line of abdominal wall.

inguinal hernia, with perforation and peritonitis, and not acute appendicitis, as we suspected at first.

## IRRADIATION IN THE TREATMENT OF CANCER OF THE BREAST\*

FREDERICK W. O'BRIEN, M.D.,† AND EUGENE McDONALD, M.D.‡

BOSTON

A DISCUSSION of the place of irradiation in the treatment of mammary cancer naturally divides itself into an attempt to evaluate the usefulness of the procedure in primary operable cases, as the sole therapeutic measure; as a preoperative procedure; as a postoperative routine; in the control of local recurrences and distant metastases; and in cases with frankly inoperable tumors.

The radiation method is based on the object of treatment, — namely, cure or palliation, — the physical setup — namely, adequate amounts of radium and roentgen-ray apparatus of accepted potential — and the experience of the radiologist. Because of the nature of this presentation, a detailed statistical analysis is not attempted.

*Irradiation Alone in Operable Cases*

Irradiation as the sole therapeutic measure is justifiable in cases, otherwise operable, in which the patient is a poor surgical risk, in the borderline operable patient and in specially organized clinics.

Since 1922, Keynes<sup>1</sup> has treated 390 selected cases of operable cancer of the breast with buried radium needles. He does not recommend their use in very advanced stages of breast cancer, cases with demonstrable distant metastases, avascular ulcerated tumors or very stout patients, since a great deal of fat in the breast and axilla makes accurate placing of the needles difficult. He considers all other cases suitable, and believes that patients in the very earliest stage of the disease are eminently suitable for radium treatment. He shows a five-year survival rate of 65.9 per cent, and he states that it is certain that many of the patients included in his Class I cases (with disease apparently confined to the breast) should really appear in Class II, that is, among those with metastatic involvement of the axillary glands. This fact suggests that if a correction for this error could be made, the statistical result in Class I would be very much better than it actually appears to be. Keynes sometimes removes the breast by diathermy. It must be remembered that his radium attack is a highly individualized surgical procedure.

We are not aware that anyone has systematically treated primary operable breast cancer with x-rays alone, except when for some reason surgical intervention has been contraindicated, and even

these cases do not run into numbers comparable with those of Keynes.

We do not believe, other things being equal, that irradiation to the exclusion of surgery should be employed in that group of patients with mammary cancers who, when operated on radically, give a five-year cure rate (alive without disease) of 70 per cent or better, as reported by Simmons and his associates.<sup>2</sup> It may be argued that this is a rigidly selected group, but that is as it should be. From our experience, it seems the part of wisdom to drop the term "operable breast cancer" and use the designation "curable cancer." The surgeon who thinks in terms of curable cancer is very much less likely to intervene in a case that is technically operable but in which operation would shorten the patient's life.

The extent of the disease, here as elsewhere, has come to be recognized as the most vital single factor influencing cure. Once the disease has extended to the axilla, the five-year cure rate by surgery drops to about 30 per cent. Less emphasis is placed on the grading of malignant tumors than formerly, for it has been shown that, regardless of the grade, if the tumor is localized and removed in its entirety, the cure rate is not affected. The grade of malignancy has, however, a prognostic value. Tumors of high malignancy are commoner in the younger age groups and are likelier to have already metastasized. These cases, for the most part, prevent a perfect surgical cure rate.

*Preoperative Irradiation*

The foregoing suggests the advisability of preoperative x-ray or radium therapy, not to supplant surgery but to complement it. Much of the criticism of preoperative irradiation has been justified. We do not believe that an inoperable cancer is made operable in the sense of curability by irradiation, but we do believe that the attempt should be made to immobilize tumors of high malignancy by judicious preoperative irradiation in an attempt to improve the cure rate of this group. And this can be done without prejudice to rather prompt surgical intervention.

The objections commonly raised against preoperative irradiation are that delay in operating creates a mental and physical hazard for the patient, and that adequate irradiation produces fibrosis, and makes the operation more difficult and the skin less likely to heal. Furthermore, if the

\*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 22, 1941.

†Chief, Tumor Clinic, Boston City Hospital.

‡Resident in radiology, Boston City Hospital.



tumor disappears under irradiation, the patient may be falsely misled into not returning for surgery; and, finally, there is no evidence to prove that preoperative irradiation is of benefit.

The last objection will always remain imposing and difficult to refute while surgeons hold out steadfastly against trial of the method. If patients are seen privately or in a tumor clinic and assured that the irradiation is in preparation for surgical excision later, no mental hazard need exist; the physical hazard already exists. If the disease has already extended to the axilla and beyond at the time of the first examination, it is difficult to reason that immediate irradiation will stimulate the spread of the disease rather than immobilize what is already there. There is no scientific evidence that irradiation stimulates tumor growth; on the contrary, there is abundant animal and human evidence that it halts neoplastic growth.

The method of administering preoperative irradiation, both the total dosage and the chronologic spacing of the unit dose, is of the greatest moment. The work of Adair and his associates<sup>3</sup> is frequently quoted in disparagement of preoperative irradiation. We agree that if one were to follow literally the method employed by Adair, one would have to expect the untoward results described by him. But it should be recalled that he intentionally used large doses of intensive radiation to obtain data on the cancerocidal effects of x-rays on the tumor in the breast and axillary nodes.

We do not believe that radiation in amounts sufficient to sterilize the tumor is either desirable or necessary after massive doses of x-radiation. Melnick and Bachem,<sup>4</sup> working with transplantable rat tumors, observed necrosis of tumor cells, hyperemia, cellular infiltration, granulation-tissue proliferation, fibrosis and blood-vessel changes, whereas after fractional and protracted methods of irradiation, only the most radiosensitive cells were destroyed by necrosis, the remaining resistant cells being transformed into tumor giant cells that degenerated not by necrosis but by calcium deposit, with no apparent effect in adjacent normal tissues. Melnick<sup>5</sup> repeated the experiments, using radon implants, with results parallel to those of the earlier study. In view of the experimental findings in animal tumors, Halley and Melnick<sup>6</sup> now prescribe preoperative irradiation extending over four or five weeks and followed by amputation within two to four weeks. A shorter preoperative course fails to obtain optimum tumor damage. The mutationlike effects, which they believe may be the most significant mechanism, require four to five weeks. Surgery done within two or three weeks of the end of irradiation has

the advantage of dealing with a tissue in which viable tumor cells have been decreased to a numerical minimum, with slight damage to the tumor bed. Delay of surgical interference beyond four weeks, according to Halley and Melnick, makes regrowth of the tumor probable. Optimum spacing of the radiation dose may well be the crux of the entire problem, as indicated in the work of Spear and Glücksmann.<sup>7</sup>

### *Postoperative Irradiation*

Routine postoperative irradiation has been abandoned in some clinics because of apparently paradoxical results, and carried on in others in the belief that the question is still *sub judice*. We are convinced that if postoperative irradiation is to be given in its commonly accepted sense of "prophylactic," many more fields of irradiation should be utilized than is the prevailing custom, as suggested by Lenz et al.<sup>8</sup> It is not sufficient to treat the affected chest wall, axilla and supraclavicular chain of lymphatics; one must treat the mediastinum and parasternal nodes, as well as the lymphatics of the opposite breast, over a protracted period.

We do not believe, however, that postoperative irradiation is necessary in those patients in whom the disease was localized in the breast by diagnostic roentgen-ray, operative and pathological examinations, with the exception of Grade III tumors, which are presumed to metastasize early. Roentgen-ray castration may be of value.

On the other hand, we are of the opinion that postoperative irradiation is definitely a useful therapeutic measure in patients whose disease appeared localized in the breast clinically but on pathological examination was found to have extended to the axillary nodes. In one series examined by us, 39 per cent of patients so classified lived over five years without demonstrable disease.

By far the largest group referred to our clinic for postoperative irradiation is made up of patients in whom the operation was frankly inadequate or of doubtful completeness. Irradiation of this group is usually only palliative, and is given with the idea of growth restraint and in the hope that if the remaining cancer cells are implanted elsewhere they may be less viable. Sometimes, physicians are critical of irradiation because it does not compensate in some miraculous way for lack of surgical judgment. Indeed, the radiation therapist has been accused of venality<sup>9</sup> when he treats these cases, whereas his confrere is pardoned for having operated on them. In our series of 50 consecutive cases of this type, 29 patients had surgery only and lived on the average nine months, whereas 21 who had surgery and irradiation lived

on the average over three years. Not a single patient in the first group lived five years, but in the latter group 5 lived for more than five years.

In 1940, a monograph<sup>10</sup> covering the treatment of cancer of the breast quoted, in censure of post-operative irradiation, statistics from a paper that appeared in 1935 based on cases operated on and irradiated from 1910 to 1929—a period when radiation therapy had hardly reached its adolescence. Many clinics during this time were treating patients with apparatus of diagnostic potential only. We believe that statistical data founded on radiation methods abandoned for more than a decade should be presented merely for what they are worth.

It should be plain that end results bear a direct relation to the criteria of operability, the extent of the disease, the degree of malignancy, the pathological interpretation, the kind of operation done, the skill of the operator and the use of any supplemental measure, such as radiation.

It is one thing to compare surgical end results in cases free of axillary nodes with similar cases that have had radiation added; it is another matter when axillary nodes or other complications are present. It is necessary to know how many patients had surgery only in the presence of skin ulceration, cutaneous nodules, supraclavicular nodes, distant metastases, secondary radical procedures, inflammatory carcinoma and lactating breasts; how many had surgery and irradiation, and when irradiation was given in relation to the operation. Much of the criticism leveled at radiation therapy is vitiated by failure to apply the principle that only like things are comparable.

#### *Irradiation for Local Recurrences and Distant Metastases*

Local recurrence in the skin or scar, when the nodules are discrete and few in number, may be excised surgically or treated by surface or interstitial radium or intensive x-radiation with a well localized field. If the nodules are multiple and contiguous, surgical removal is not usually advisable because of the loss of skin entailed thereby. In this situation, high voltage x-rays or radium when available in sufficient quantity is preferable.

The appearance of secondary nodules in the scar or skin of the breast area usually means that the extirpation of the mammary gland was not wide enough. Hicken<sup>11</sup> has shown by mammographic studies that the lactiferous ducts spread over the entire anterolateral wall of the chest. Examining breasts supposed to have been completely

excised by "mastectomy procedures" after injection of the ducts with a solution of methylene blue, he did not find a single case in which the mammary tissue had been removed in its entirety. In 94 per cent of the cases, the dye escaped in the subareolar zone, indicating that some of the breast had been left attached to the reflected skin flaps.

In an earlier study of 255 cases of breast cancer, one of us (F W O B<sup>12</sup>) found recurrence in the skin or scar in 21 per cent of the cases. The appearance time of the local recurrence in this group seemed directly related to the completeness of the surgical excision and the extent of the disease at the time of operation, rather than to the kind of tumor.

Distant metastases, on the other hand, involve other factors than completeness of operation and extent of the disease. They occur when, according to the rules of the game, they should not. In such cases, the kind of tumor and its method of spread by the lymphatics or vertebral veins seem of significance. The estrogenic theory of multiple foci of origin must also be considered when one discusses what seems to be a metastasis but what in reality may be one of several primary foci.

Often enough, metastases that are presumed to be postoperative were present at the time of surgical intervention. It is safe to assume that bone metastasis demonstrable by x-ray study ten days after operation has been present for a much longer period. In the records of more than 50 per cent of one series examined by us, there was no evidence of preoperative diagnostic x-ray examination. Roentgenologic study of the chest, spine and pelvis should be made before operation, as White<sup>13</sup> counsels, without regard to the smallness of the primary tumor, lack of nodes or suggestive symptoms. When this procedure is employed, many cancers clinically localized prove to be diffuse and inoperable.

Distant metastases may be controlled for long periods by appropriate gamma radiation or high voltage x-rays. In suspected bone metastasis, irradiation should be promptly directed to the site of pain irrespective of negative diagnostic x-ray examination. The entire vertebral column may be riddled with tumor, without demonstrable roentgenologic findings. Any orthopedic appliance used in the presence of collapse of the vertebral bodies or fracture of the long bones that will preclude irradiation, since new bone formation often enough follows its application, should be interdicted. Occasionally, generalized skeletal

metastases have disappeared completely following irradiation of the ovaries.

Pleural effusion sometimes resolves after relatively small doses of medium-voltage x-ray therapy, and the progress of lung metastasis is halted by fibrosis deliberately produced by the employment of supervoltage radiation. Such therapy is palliative, to be sure, but it is comparable in some measure with therapeusis in certain other chronic but fatal maladies common to the field of internal medicine.

#### *Irradiation of Inoperable Tumors*

The inoperable cases are cheerfully passed on to the radiation therapist. Although such cases are hopeless as a group, enough palliative benefit ensues to justify acceptance of such patients when they are not in extremis. Ulcerating breasts frequently heal, axillary and supraclavicular nodes regress, but secondary deposits appear in the skeleton or other organs. Care should be exercised that these patients have proper medical follow-up. A judicious use of sedatives, antianemic remedies and relatively small doses of radiation help a few to live in comparative comfort for five years or longer.

\* \* \*

In conclusion, we do not claim that irradiation is in competition with surgery. We wholeheart-

edly subscribe to the dictum that any surgeon who does less than a radical operation in curable breast cancer is not giving his patient even a sporting chance for recovery. Likewise, we believe that the surgeon who studiously condemns irradiation on statistical data derived from cases treated just after the turn of the century, when the limits of surgical curability were ill defined and radiation therapy was still undeveloped, denies to his patient a therapeutic aid to longer life.

#### REFERENCES

1. Keynes, G. The place of radium in the treatment of cancer of the breast. *Ann. Surg.* 106:619-630, 1937.
2. Simmons, C. C., Taylor, G. W., and Welch, C. E. Carcinoma of the breast. *Surg., Gynec. & Obst.* 69:171-177, 1939.
3. Adair, F. E. The effect of preoperative irradiation in primary operable cancer of the breast. *Am. J. Roentgenol.* 35:359-370, 1936.
4. Melnick, P. J., and Bachem, A. The time factor in the irradiation of malignant tumors. *Arch. Path.* 23:757-792, 1937.
5. Melnick, P. J. Unpublished data.
6. Halley, E. P., and Melnick, P. J. Preoperative irradiation in carcinoma of the breast. *Radiology* 35:430-438, 1940.
7. Spear, F. G., and Glücksmann, A. The effect of gamma radiation on cells *in vivo*. *Brit. J. Radiol.* 14:65-76, 1941.
8. Lenz, M., Frantz, V. K., and Kasabach, H. H. Prophylactic postoperative roentgentherapy for carcinoma of the breast. *New York State J. Med.* 34:881-887, 1934.
9. Wolfer, J. A. Book review: *Treatment of Cancer and Allied Diseases. Surg., Gynec. & Obst.* 71:534, 1940.
10. Pack, G. T., and Livingston, E. M. *Treatment of Cancer and Allied Diseases*. 1500 pp. Vol. 1. New York and London: Paul B. Hoeber, Inc., 1940.
11. Hicken, N. F. Mastectomy: a clinical pathologic study demonstrating why most mastectomies result in incomplete removal of the mammary gland. *Arch. Surg.* 40:6-14, 1940.
12. O'Brien, F. W. Skin metastasis in post-operative irradiated breast cancer. *Radiology* 30:437, 1938.
13. White, W. C. Irradiation as an aid to surgical treatment of cancer of the breast. *J. A. M. A.* 110:261-265, 1938.

## MEDICAL PROGRESS

### MEDICAL ASPECTS OF OBSTETRICS

JUDSON A. SMITH, M.D.\*

BOSTON

OF THE medical complications of pregnancy, the most important are those conditions characterized by hypertension and albuminuria and often loosely grouped under the old-fashioned and misleading designation "toxemias of pregnancy." In 1940, the American Committee on Maternal Welfare adopted a classification of these toxemias that now seems to be gaining acceptance by obstetric clinics throughout the country. It was presented with a detailed explanation in a recent paper by Mussey and Hunt<sup>1</sup> and is given below in a slightly condensed form.

#### GROUP A Diseases not peculiar to pregnancy

##### I Hypertensive disease (hypertensive cardiovascular disease)

- a Benign (essential)
- b Malignant

##### II Renal Disease

- a Chronic vascular nephritis or nephrosclerosis
- b Glomerulonephritis
- c Nephrosis
- d Other renal disease (such as pyelonephritis)

#### GROUP B Disease dependent on, or peculiar to, pregnancy

##### I Pre-eclampsia

- a Mild
- b Severe

##### II Eclampsia

- a Convulsive
- b Nonconvulsive (that is, with coma and post mortem findings typical of eclampsia)

This classification is entirely logical in theory, if one accepts the underlying assumption that there is a specific hypertensive disease peculiar to pregnancy. Group A is composed of cardiovascular and renal diseases that occur independently of pregnancy and whose association with pregnancy is therefore a matter of chance. Group B consists of a single disease, which is in some way caused by pregnancy and which is referred to as pre-eclampsia or eclampsia according to the severity of the symptoms. The persistent belief that eclampsia is a pathologic entity has rested mainly on three facts: it occurs in women who have never

previously shown evidence of cardiovascular or renal disease, it not infrequently results in complete recovery, leaving no demonstrable evidence of impairment of the cardiovascular system or kidney, and its typical picture has not been observed apart from pregnancy.

The actual classification of individual cases according to the above scheme, at least during pregnancy, is often difficult or impossible, largely because there is no readily available diagnostic test by which pre-eclampsia can be recognized. We are forced to rely on two empirical facts: eclampsia rarely, if ever, occurs before the sixth lunar month, and pre-existing vascular or renal disease is usually definitely aggravated by the pregnancy before the sixth month. The twenty-fourth week, therefore, is arbitrarily taken as a dividing line. Hypertension appearing before that time is regarded as *prima facie* evidence of a pre-existing disease independent of the pregnancy, hypertension appearing after the twenty-fourth week in a woman who has no history of vascular or renal disease is regarded as *prima facie* evidence of pre-eclampsia. These criteria, of course, are not perfectly satisfactory. If, for example, a patient with pre-existing mild vascular hypertension becomes worse later in pregnancy, it is difficult to decide whether the original disease is aggravated or she is beginning to develop superimposed pre-eclampsia. Furthermore, in cases of mild hypertension appearing soon after the twenty-fourth week and remaining mild, it is usually impossible to determine whether the condition is delayed aggravation of a pre-existing vascular or renal disease or a mild subacute pre-eclampsia. As a practical rule in the management of these cases, however, it is always safer to regard acute exacerbations of hypertension or albuminuria as indicative of pre-eclampsia.

The distribution of these conditions, when classified as above, is shown in Table 1, which is taken from a recent study by Irving<sup>2</sup> of 1182 consecutive cases of hypertension and albuminuria in pregnancy.

During the past year, Smith, Smith and Schiller<sup>3</sup> have made an extremely interesting and valuable contribution to the study of the etiology of pre-eclampsia. They measured the levels of pregnanediol, estradiol, estrone and estriol and the es-

Reprints of articles in this series are not available for distribution but the articles will be published in book form. The current volume is *Medical Progress Annual 1940* (Springfield III no. 5 Charles C Thomas Company 1941 \$4.00).

\*Instructor in obstetrics Harvard Medical School assistant obstetrician Boston Lying in Hospital obstetrician Massachusetts General Hospital

trogenic potency after hydrogenation in the urines of 22 patients with pre-eclampsia and eclampsia and of 15 normal women during the last tri-

TABLE 1. *Diagnosis in 1182 Consecutive Cases of Hypertension and Albuminuria in Pregnancy.*

DIAGNOSIS	NO. OF CASES	PER CENT
Essential hypertension .....	68	5.8
Chronic renal disease .....	13	1.1
Pre-eclampsia, mild .....	889	75.0
Pre-eclampsia, severe (including 13 cases of eclampsia) .....	212	18.1

mester. The results indicated that pre-eclampsia is associated with a progressive deficiency of progesterin, which results in a greater and more rapid destruction of estrogens. They consider this derangement of estrogen metabolism to be due to disturbed placental function, which, they point out, might result from numerous mechanical or organic interferences with placental blood supply. Their ideas of the relation between the changed estrogen metabolism and symptoms of pre-eclampsia are best expressed in their own words:

We are convinced that the significant finding, so far as the clinical manifestations of pre-eclampsia and eclampsia are concerned, is the sudden, rapid destruction of estrogens. The menstrual phenomenon has also been found to be accompanied by the same evidence for rapid destruction of the estrogens following estrogen and progesterin withdrawal. Furthermore, there is a striking similarity between the local changes in the premenstrual endometrium and the generalized disturbances so characteristic of pre-eclampsia and eclampsia. The menstrual discharge has been found to contain a potent toxin to the action of which we would attribute the local changes resulting in menstruation. The formation of this toxin appears to be closely allied to rapid destruction of the estrogens. By analogy, we would postulate that the same shift of steroid metabolism in pregnancy results in the formation, on a larger scale, of a similar toxin, possibly in the decidua. The albuminuria of pre-eclampsia might be ascribed to the effect of such a toxin acting on the kidney glomeruli, the hypertension to an actual Goldblatt phenomenon from renal arteriolar constriction due to the same toxin, and edema to an effect upon capillaries similar to that which takes place in the premenstrual endometrium.

Having arrived at these admittedly speculative conclusions, they tested them by treating a small series of patients with pre-eclampsia with daily injections of estrogen and progesterin. The resulting shift toward normal in both the clinical manifestations and the hormonal changes was considered sufficient to bear out their theory. The authors noted, however, that the difficulty and expense of giving adequate daily doses of these hormones, for the present at least, preclude their use as a practical therapeutic measure.

Some newer methods of studying renal function have revived interest in this aspect of the hypertensive complications of late pregnancy. The

phenolphthalein excretion, concentration test and urea clearance are usually normal in both essential hypertension and pre-eclampsia. When, however, the renal blood flow per unit of time and the filtration fraction are determined, certain deviations from normal appear.

By the filtration fraction is meant the proportion of plasma that is filtered through the walls of the glomerular capillaries into Bowman's capsule—that is, the ratio of the amount of the glomerular filtrate during a certain time to the amount of plasma that flowed through the kidneys during the same period. To determine the plasma flow, use is made of the fact that Diodrast, at low concentration in the plasma, has a renal-excretion ratio of very nearly 100 per cent. In other words, of all the Diodrast carried to the kidney by the renal artery, none escapes by the renal vein. Thus, measurement of the plasma level of Diodrast and of the amount excreted per minute permits calculation of the amount of plasma that has flowed through the kidneys. The volume of the glomerular filtrate can be measured simultaneously by determining the ratio of the quantity of inulin excreted each minute to the plasma level of inulin, since inulin is neither excreted nor absorbed by the cells of the tubules. The normal filtration ratio is about 0.20.

Corcoran and Page<sup>4</sup> have studied a series of late toxemias of pregnancy by these methods and report that there are three groups. In Group I, the plasma flow was diminished, and the filtration fraction was increased. These findings are consistent with constricted efferent arterioles and normal capillaries, and are characteristic of essential hypertension in the nonpregnant woman. The patients in this group presented the clinical picture of pre-existing or latent essential hypertension. In Group II, the filtration fraction was low, and the clinical picture was that of severe pre-eclampsia or eclampsia. Corcoran and Page suggest that a lowered filtration fraction is the physiologic manifestation of the swelling of the basement membrane of the glomerular capillaries, which is generally regarded as the characteristic renal lesion of pre-eclampsia and eclampsia. In Group III, the filtration fraction was normal, and the clinical manifestations were mild. The authors do not attempt to classify these cases but believe that many of them represent mild pre-eclampsia.

Chesley<sup>5</sup> has reported similar findings and has come to similar conclusions. He believes that the lowered filtration fraction indicates severe glomerular damage, and suggests that, if pre-eclampsia or eclampsia is a cause of subsequent hypertension, the patients with a marked lowering of the filtration fraction should show a high incidence of hypertension later. In his series of 10 cases, 4 pa-

tients were hypertensive—that is, they had blood pressures above 140 systolic, 90 diastolic—two years later. He also reports observations on 7 patients with normal blood pressure one to four years after severe pre-eclampsia or eclampsia. In several cases, there was a marked deficit in renal blood flow, and in 2 cases a marked lowering of the filtration fraction. Chesley suggests that in some of these cases, in spite of the absence of hypertension, there may be glomerular damage.

The frequency with which a so called "toxic" pregnancy is followed by essential hypertension or chronic cardiovascular disease has been repeatedly pointed out in the last few years. The most recent contribution of this sort is a statistical study by Peckham<sup>6</sup> of 500 such patients observed throughout pregnancy and subsequently followed from two to ten years. For inclusion in this group, it was required that the patient should have made a minimum of three visits to the clinic, at each of which the blood pressure and urine were normal. This resulted in the selection of a group of patients none of whom showed evidence of toxemia before the fourth lunar month. Of the entire group, 63 per cent were found to have chronic vascular damage. The series was divided first according to the month of onset of toxemia and then according to the time elapsed between the onset and delivery. It was found that the incidence of permanent damage was greater the earlier the onset and the longer the time between onset and delivery. Peckham believes the latter factor to be the more significant in prognosis and suggests that four weeks should be the maximum period of observation of the toxic patient, ignoring, apparently, the problem of the viability or nonviability of the fetus. A complete discussion of these statistics is impossible, but attention must be directed to one point concerning the apparent effect of long duration of the toxemia, namely, that the longer the time elapsed between the onset of toxic symptoms and delivery, the likelier it is that the clinical picture was the type to suggest latent pre-existing vascular disease rather than pre-eclampsia.

There has been no progress in the therapy of the toxemias of pregnancy. Goethals<sup>7</sup> last year discussed the treatment of eclampsia with veratrum viride, as reported by Bryant and Fleming.<sup>8</sup> If there have been any further reports of the use of this drug they have escaped my notice. Nicodemus<sup>9</sup> describes the treatment of 13 eclamptic patients with the oxygen tent; all recovered. Although this result is of no statistical significance, the idea seems, a priori, to be worthy of trial.

Numerous reports<sup>10-18</sup> have recently been published that add to the evidence of the effectiveness of Vitamin K in preventing hemorrhagic disease of the newborn. The ideal method of prophylaxis seems to be the parenteral adminis-

tration of Vitamin K to the mother at the onset of labor and to the infant immediately after birth. There can no longer be any excuse for neglecting this precaution. Javert and Macri<sup>19</sup> present some evidence suggesting that the daily ingestion of mineral oil leads to a deficiency of Vitamin K in pregnant women by preventing absorption.

There is nothing to be added to the chemotherapy of puerperal sepsis except the introduction of a new analogue of sulfanilamide, namely, sulfadiazine. Long,<sup>20</sup> who has made a preliminary report on this drug, finds that it is somewhat less rapidly absorbed from the gastrointestinal tract than sulfanilamide, sulfapyridine and sulfathiazole, and that it is somewhat less rapidly excreted than sulfanilamide or sulfapyridine, when renal function is normal. It is relatively easy to maintain an adequate concentration of the drug in the blood, and as a matter of fact, the blood level must be followed carefully to prevent unnecessarily high concentrations. It produces very little nausea and vomiting and appears to be less apt to cause drug fever and drug rash than sulfanilamide, sulfapyridine and sulfathiazole. Up to the time of his report, Long had observed no cases of renal injury. Its effectiveness in hemolytic streptococcus infections compares favorably with that of sulfanilamide. As yet, there has not been sufficient experience with sulfadiazine to make its evaluation possible.

Heckel<sup>21</sup> discusses the possibility that chemotherapy during pregnancy and the puerperium may injure the fetus in utero or the nursing infant. He considers injury to the nursing infant from sulfanilamide extremely unlikely. This drug is excreted in the milk in a concentration approximating that in the blood. A nursing infant consequently can get only a minute dose from its mother's milk. Babies nursed by mothers receiving 4 gm. a day showed only traces of the drug in the blood and behaved quite normally. Injury to the fetus is theoretically possible, since there is evidence that the concentration of sulfanilamide in the fetal blood is equal to that in the mother's within a few hours after administration. Heckel reports results in 13 women who were given chemotherapy at various stages of pregnancy and followed through delivery. Twelve of the infants were normal. One infant had a moderately severe anemia, for which no cause could be found. Heckel suggests that the anemia might have been due to the sulfanilamide administered to the mother. She had received daily doses (maximum, 30 gr.) to a total of about 750 gr. over a period of thirty seven days, terminating fifteen days before delivery. Whatever the chances of injury to the fetus may be, they are no greater, he believes, with large doses than with small ones.

Steiner and Lushbaugh<sup>22</sup> believe that they have

recognized a new obstetric disease. They report 8 cases of unexpected and rather sudden maternal death during labor or soon after delivery. Clinically, the symptoms were those of severe shock. In some cases, there was atony of the uterus and post-partum hemorrhage, but only after the appearance of shock. In some cases, there was acute pulmonary edema. The essential pathologic condition was found on microscopic examination to be widespread embolism of small pulmonary arteries, arterioles and capillaries by the particulate matter found in amniotic fluid and by meconium. They have duplicated the disease clinically and pathologically in rabbits and dogs by the intravenous injection of human amniotic fluid and meconium. Three of their cases were found at the Chicago Lying-in Hospital over a period of nine years, during which time there were 24,200 deliveries, an incidence of 1 in about 8000 deliveries.

Some recent discoveries in connection with intragroup transfusion reactions are of great interest to obstetricians. The subject of isoimmunization in relation to intragroup reactions has been completely presented in a progress report by Hooker.<sup>23</sup> The facts that are of interest to the obstetrician concern the atypical agglutinin, which has been named the Rh factor (because it occurs in the blood of the *Macacus rhesus* monkey) and which is present in the red cells of about 86 per cent of human bloods.<sup>24</sup> Persons who have this factor in their red cells are Rh+; the 14 per cent of persons who lack it are Rh-. Since the Rh factor is inherited according to the Mendelian law as a dominant,<sup>25</sup> the children of an Rh- mother and an Rh+ father will all be Rh+ if the father is homozygous with respect to this factor. If the father is heterozygous with respect to the Rh factor, half the children will be Rh+. The frequency of such marriages (Rh- wife, Rh+ husband), if due to chance alone, should obviously be about 12 in 100. There is now convincing evidence<sup>26, 27</sup> that sometimes when an Rh- woman is carrying an Rh+ fetus in her uterus, Rh antigen from the fetal blood gains access to the maternal blood and stimulates the production of antibodies; the maternal antibodies readily diffuse into the fetal circulation, destroying fetal red cells and producing the disease known as erythroblastosis foetalis. From these facts, it is apparent that if the mother of an erythroblastotic child is transfused with blood from her Rh+ husband or from any other Rh+ donor, there is grave danger of a reaction. A number of such reactions have been reported—some fatal.<sup>27</sup> It must be borne in mind that this is an intragroup reaction—ordinary direct cross-matching of bloods will not detect the incompatibility. It can be detected, however, by incubating a mixture of recipient's

serum and donor's cells at 37°C. for thirty minutes.<sup>28</sup> This precaution (incubation) in cross-matching, therefore, becomes imperative in the selection of donors for all pregnant and parous women. If incompatibility is found, it will be necessary to determine at once the Rh status of the woman. If she is Rh- and her blood contains anti-Rh antibodies, she can be safely transfused only from a donor in the correct blood group who is also Rh-. Since finding such a donor might take some time, maternity clinics should have lists of donors whose Rh status has been determined. It is well to remember, if one is in a hurry for an Rh- donor, that since the character of being Rh- is a recessive, a brother or sister of the Rh- patient is much likelier to be Rh- than a donor selected at random.

264 Beacon Street

## REFERENCES

1. Mussey, R. D., and Hunt, A. B. The toxemias of pregnancy and the management of parturition. *J. A. M. A.* 117:1309-1313, 1941.
2. Irving, I. C. A study of consecutive cases of hypertension and albuminuria in pregnancy. *Pennsylvania M. J.* 44:557-562, 1941.
3. Smith, O. W., Smith, G. V., and Schiller, Sara. Estrogen and progestin metabolism in pregnancy. *J. Clin. Endocrinol.* 1:461-476, 1941.
4. Corcoran, A. C., and Page, I. H. Renal function in late toxemia of pregnancy. *Am. J. M. Sc.* 201:385-396, 1941.
5. Chesley, L. C. The question of glomerular damage following toxemia of pregnancy. *Am. J. Obst. & Gynec.* 42:229-235, 1941.
6. Peckham, C. H. Time of onset and duration of the toxemias of late pregnancy in relation to the development of permanent vascular damage. *Am. J. Obst. & Gynec.* 42:638-645, 1941.
7. Goethals, T. R. Medical aspects of obstetrics. *New Eng. J. Med.* 224:200-204, 1941.
8. Bryant, R. D., and Fleming, J. G. Veratrum viride in the treatment of eclampsia. *J. A. M. A.* 115:1333-1339, 1940.
9. Nicodemus, R. E. Oxygen tent therapy in the treatment of eclampsia. *J. A. M. A.* 117:1238, 1941.
10. McCready, R. L., Callahan, E. T., and Grandin, D. J. Parenteral vitamin K therapy in ante-partum women and its effects on the infants' prothrombin level. *Am. J. Obst. & Gynec.* 42:398-404, 1941.
11. Javert, C. T., and Macri, C. Prothrombin concentration in normal pregnancy. *Am. J. Obst. & Gynec.* 42:415-419, 1941.
12. Andrus, W. DeW. The newer knowledge of vitamin K. *Bull. N. Y. Acad. Med.* 17:116-134, 1941.
13. Maumence, A. E., Hellman, L. M., and Shettles, L. B. Factors producing plasma prothrombin in the newborn infant. IV. The effect of antenatal administration of vitamin K on the incidence of retinal hemorrhage in the newborn. *Bull. Johns Hopkins Hosp.* 68:158-168, 1941.
14. Bohlender, G. P., Rosenbaum, W. M., and Sage, E. C. Antepartum use of vitamin K in the prevention of prothrombin deficiency in the newborn. *J. A. M. A.* 116:1763-1766, 1941.
15. Huber, C. P., and Shrader, J. C. Blood prothrombin levels in the newborn. *Am. J. Obst. & Gynec.* 41:566-574, 1941.
16. Mull, J. W., Bill, A. H., and Skrowronska, H. Effect on the newborn of vitamin K administered to mothers in labor. *J. Lab. & Clin. Med.* 26:1305-1309, 1941.
17. Beck, A. C., Taylor, E. S., and Colburn, R. F. Vitamin K administered to the mother during labor as a prophylaxis against hemorrhage in the newborn infant. *Am. J. Obst. & Gynec.* 41:765-775, 1941.
18. Edsall, G. The prothrombin level in early infancy: its relation to hemorrhage and other neonatal disturbances. *New Eng. J. Med.* 224:762-766, 1941.
19. Javert, C. T., and Macri, C. Prothrombin concentration and mineral oil. *Am. J. Obst. & Gynec.* 42:409-414, 1941.
20. Long, P. H. Sulfadiazine. *J. A. M. A.* 116:2399, 1941.
21. Heckel, G. P. Chemotherapy during pregnancy. *J. A. M. A.* 117:1314-1316, 1941.
22. Steiner, P. E., and Lushbaugh, C. C. Maternal pulmonary embolism by amniotic fluid: as a cause of obstetric shock and unexpected deaths in obstetrics. *J. A. M. A.* 117:1245-1254 and 1340-1345, 1941.
23. Hooker, S. B. Isoimmunization in relation to intragroup hemolytic transfusion reactions. *New Eng. J. Med.* 225:871-877, 1941.
24. Landsteiner, K., and Wiener, A. S. An agglutinable factor in human blood recognized by immune sera for rhesus blood. *Proc. Soc. Exper. Biol. & Med.* 43:223, 1940.
25. Landsteiner, K., and Wiener, A. S. Studies on an agglutinin (Rh) in human blood reacting with anti-rhesus sera and with human iso-antibodies. *J. Exper. Med.* 74:309-320, 1941.
26. Levine, P., Katzin, E. M., and Burnham, L. Isoimmunization in pregnancy. *J. A. M. A.* 116:825-827, 1941.
27. Burnham, L. The common etiology of erythroblastosis and transfusion accidents in pregnancy. *Am. J. Obst. & Gynec.* 42:389-397, 1941.
28. Levine, P. The role of iso-immunization in transfusion accidents in pregnancy and in erythroblastosis foetalis. *Am. J. Obst. & Gynec.* 42:165, 1941.

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTE-MORTEM AND POST-MORTEM RECORDS AS USED  
IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

CASE 28011

### PRESENTATION OF CASE

A sixty-three-year-old housewife, formerly a factory worker, was admitted to the hospital because of jaundice, malaise, nausea, vomiting, weakness and abdominal discomfort.

She had been in excellent health until four years before admission, when she began to have intermittent episodes of malaise, nausea and vomiting, chills, slight jaundice and frontal headaches, which lasted about two weeks and recurred at intervals varying from two weeks to six months. The earliest attacks were apparently precipitated by the eating of fatty foods, which had thenceforth been carefully avoided. During the attacks, the urine was dark, and the stools were frequently light colored. There was remission of jaundice between the episodes, with return to normal-appearing dejecta. The first few spells were accompanied by dull pains in the hips and back, but there were no such pains subsequently. In the few months preceding admission, the bouts of illness became severer and more frequent, and marked weakness began to appear. In the course of the four years, there was a loss of about 70 pounds in weight.

At no time in the illness was there hematemesis, melena or obvious fever. The patient denied any medication other than proprietary preparations of "bile salts" and "liver pills," prescribed by her physician.

The last episode started on an afternoon eleven days before entry, with abrupt onset of nausea and vomiting, followed by increasing malaise, weakness, jaundice and passage of dark urine. On the next day, the patient experienced shaking chills lasting for two or three hours; she did not feel feverish. In the following days, the chills recurred. Most of the stools were light colored, but some were green. There was progressive weakness, much severer than that on any previous occasion. Three or four days before entry, the abdomen became swollen and tender.

A brother of the patient had died of tuberculosis at the age of twenty-seven (when the patient was eighteen years old). The past history was otherwise of no interest. Until eight months

before entry, the patient had worked in a factory, putting linings in shoes. She knew of no exposure to chemicals or fumes. She denied the use of alcohol.

On admission, the patient appeared emaciated, quite uncomplaining and free of discomfort. There was moderate icterus of the skin and scleras. The chest was emphysematous, with rales and slight dullness at the pulmonary bases. The size of the heart was within normal limits; the heart sounds were slightly distant. The abdomen was moderately distended and tympanitic, with shifting dullness and a demonstrable fluid wave. There were moderate external hemorrhoids. The skin showed diffuse, slight edema.

The temperature was 100°F., the pulse 110, and the respirations 24. The blood pressure was 118 systolic, 70 diastolic.

Examination of the blood showed a red-cell count of 4,150,000 with 13.7 gm. hemoglobin, and a white-cell count of 10,600 with 88 per cent polymorphonuclears. The blood Hinton reaction was negative. The van den Bergh reaction was biphasic, and showed 4.6 mg. bilirubin per 100 cc. The blood cholesterol was 172 mg. per 100 cc. The phosphatase was 25.7 Bodansky units, and the phosphorus 2.8 mg. per 100 cc. The serum albumin was 2.7 gm. and the serum globulin 4.0 gm. per 100 cc. The prothrombin time was normal. The hematocrit was 39.3 per cent. The bromsulfalein test showed 50 per cent dye retention.

The urine was normal except for the finding of bile by the foam test. The stools were pasty and soft green, with a positive guaiac reaction.

A roentgenogram of the chest showed elevation of the right diaphragm, with haziness in the right costophrenic angle. There were several areas of calcification in the right lower-lung field and hilus. Fluoroscopy demonstrated limited motion of the right diaphragm, in the correct direction, and absence of fluid in the right costophrenic angle. The diaphragm appeared pushed up by the liver. A roentgenogram of the abdomen showed enlargement of both the liver and spleen. There was no evidence of dilatation of bowel loops. The Graham test was positive.

On the sixth hospital day, a peritoneoscopy was performed.

### DIFFERENTIAL DIAGNOSIS

DR. F. DENNETTE ADAMS: It seems unlikely that the chills reported were, in the strict sense of the word, real chills, for these do not last so long as two or three hours—nor do they often come more than twice daily. I should be inclined to interpret them as the chilly sensations that accompany rises of temperature.



Nothing is said about the size of the liver and spleen on palpation; enlargement of either or both could well have been overlooked because of unsatisfactory palpation due to abdominal distention. Before proceeding, we might learn from Dr. Lingley whether he believes that these organs were enlarged.

DR. JAMES R. LINGLEY: This is the film of the chest, showing the high right diaphragm with a shallow costophrenic angle. The lower hepatic border is not well visualized, but the liver is probably enlarged. The spleen, however, is not appreciably increased in size. The gall bladder is not visualized on any of the films, and the Graham test is therefore positive.

DR. ADAMS: I shall consider this problem first from the standpoint of jaundice. The causes of jaundice may be classified as hematogenous, obstructive and hepatogenous. Hematogenous jaundice, in this case, can be readily excluded. We are obviously not dealing with such disturbances as pernicious anemia, severe generalized sepsis and familial hematogenous jaundice. Stone in the common duct and cancer account for most cases of obstructive jaundice. If this patient had cancer of the head of the pancreas, lymph-node enlargement, which might occur in lymphoblastoma, or cancer of the biliary tract interfering with the flow of bile, the jaundice would have been progressive, not intermittent, and by this time would have been severer than the findings in this case indicate. Furthermore, the gall bladder would have been large and, even with the abdomen distended, might have been palpable. The duration of the illness was long for cancer. Stone in the common duct will be considered later.

Of the hepatogenous causes, one must consider some acute intrahepatic process such as catarrhal jaundice or toxic hepatitis, cirrhosis of the liver, diffuse neoplastic disease of the liver, such as lymphoma or carcinoma, and cholangitis with ascending infection into the liver. The duration was too long for any acute intrahepatic process, and diffuse neoplastic disease can be excluded by the same line of reasoning that I have applied to cancer involving the bile passages.

Of the various forms of cirrhosis, one need hardly consider that due to syphilis or cardiac disease, or pigment cirrhosis (hemachromatosis). There is nothing to point toward any of these.

Portal and biliary cirrhosis require further thought. The history is not suggestive of portal cirrhosis. There is no record of a previous acute liver ailment, nor is there any mention of alcoholism. The only suggestive points in favor of portal cirrhosis are the ascites and the laboratory

evidence of impaired liver function. Bouts of pain simulating gall-bladder colic are not infrequently encountered in portal cirrhosis, but on the other hand, jaundice is not usually a feature except in the terminal stages.

The history of recurrent episodes of pain, jaundice, fever and gastrointestinal disturbance is perfectly typical of biliary cirrhosis. It is also typical of common-duct stone with intermittent obstruction. But biliary cirrhosis rarely occurs except in the presence of long-standing biliary-tract disease.

The laboratory tests — especially the high blood phosphatase, the low serum protein and the diminished excretion of bromsulfalein — indicate an appreciable degree of liver impairment, more than one would expect with common-duct stone alone unless the jaundice were of greater degree. By x-ray examination, the liver appeared large; the spleen may have been slightly enlarged — added evidence in favor of liver disease.

Since it seems impossible to explain all the changes on the basis of common-duct stone, one is forced to the conclusion that cirrhosis existed; if so, it must have been of the biliary type. But the presence of biliary cirrhosis presupposes previously existing obstruction or infection, and these would most probably be the result of stone in the common duct. The most likely diagnosis, then, in my opinion, is chronic cholecystitis with stones, stone in the common duct, ascending biliary-tract infection secondary to obstruction, and biliary cirrhosis secondary to the ascending infection.

One other problem deserves brief consideration. Could there have been carcinoma of the liver in addition? Primary carcinoma of the liver is not uncommon in cirrhosis and is rarely seen without cirrhosis. It is not commonly diagnosed ante mortem. One can suspect its presence in cases of cirrhosis when a definite mass can be felt in the liver, when a localized bulge of the diaphragm is discovered roentgenologically, or when metastatic cancer is discovered elsewhere. There was no evidence of metastasis, and the only hint of cancer in this case might be obtained from the roentgenologist. Dr. Lingley, should you consider the elevation of the diaphragm general, or do you think there is a localized bulge?

DR. LINGLEY: I should consider it either an enlarged liver or an infectious process beneath the dome of the diaphragm producing elevation and limitation; no definite localized bulge is apparent.

DR. ADAMS: Then I shall not add a diagnosis of primary carcinoma of the liver.

DR. TRACY B. MALLORY: Does anyone want to ask any questions or give suggestions at this point?

**A PHYSICIAN:** It seems to me that we should give serious consideration to the possibility that this was carcinoma of the ampulla of Vater. That might explain the absence of pain and the itching, and waxing and waning frequently goes with it.

**DR. MALLORY:** The presence of a large amount of ascites with biliary cirrhosis would bother me a little bit.

**DR. ADAMS:** It bothered me. Ascites is, of course, not common in biliary cirrhosis except in the terminal stages. Barring portal cirrhosis, which I do not believe existed in this case, I should say that the ascites is much more suggestive of carcinoma, but the evidence in favor of common-duct stone and biliary cirrhosis outweighs the doubt introduced by the ascites. Except for the ascites, the picture is typical of common-duct stone.

**DR. WYMAN RICHARDSON:** If you will believe me, the patient did have ascites. I am sure of it.

**DR. ADAMS:** It is too late for me to go on the other side.

**DR. MALLORY:** Dr. Richardson, do you want to comment before or after we have heard the peritoneoscopic findings?

**DR. RICHARDSON:** I should like to read the note that I made before peritoneoscopy was done. I think that is the fairest way. "Because of the history, I believe that this patient has had recurring biliary infection, perhaps with stone and with secondary biliary cirrhosis. She may have had recurring cholangitis and recurring focal liver degeneration, followed by distortion and ascites (end stage of toxic hepatitis)." I am attempting to explain the ascites, but rather poorly. "In spite of weight loss, in addition to high phosphatase, I doubt malignant tumor. If present, it must be secondary to primary liver disease, such as cirrhosis; and I cannot make out that the patient has a primary cirrhosis. Advise peritoneoscopy."

**DR. MALLORY:** Dr. Benedict, will you tell your gross findings?

**DR. EDWARD B. BENEDICT:** I shall read my report: "Under local anesthesia, a 1-cm. incision was made in the midline just above the umbilicus, the peritoneal cavity inflated with air, and the Ruddock peritoneoscope introduced. Ten pints of slightly cloudy, straw-colored fluid was aspirated and sent to the laboratory. There were many adhesions between the edge of the liver and the abdominal wall. The liver did not appear enlarged. Multiple cystic implants were visible throughout the peritoneum—on the round ligament, on the wall of the bowel, on the brim of the pelvis and throughout the pelvis. There was also a cystic appearance to the surface of the liver, as if that also were involved in the process. The

uterus was quite freely movable when examined by vagina and by rectum by Dr. McGahey. There were cystic implants on the surface of the uterus and on the broad ligaments. The ovaries could not be brought into view. There was considerable hemorrhagic appearance to the metastatic disease of the anterior abdominal wall overlying the lower abdomen and pelvis. Biopsy specimens were obtained from implants in the pelvis and from an area of the anterior peritoneum overlying the liver."

**DR. MALLORY:** What was your impression at the end?

**DR. BENEDICT:** General carcinomatosis.

**DR. MALLORY:** Dr. Benedict's various biopsy specimens were examined histologically, and all of them showed tuberculosis.

**DR. RICHARDSON:** I shall read one further note, which I wrote after the peritoneoscopy: "I am not satisfied with the diagnosis of tuberculosis in this patient." I did not mean to say that I doubted the pathologist. I believed that the patient must have had tuberculosis, but that something else was present. I said: "If it is present, there must be another pathologic process. I believe that it is most probably tumor. There may also be cirrhosis of the liver." That is as far as I went.

**DR. MALLORY:** Do you want to make a further diagnosis, Dr. Adams?

**DR. ADAMS:** I am very grateful for Dr. Richardson's support. I fail to see how tuberculous peritonitis can explain the whole picture. Nor can I make any diagnosis other than the one I have already made, on the basis of the evidence provided by the protocol. How could the jaundice be explained by tuberculous peritonitis?

**DR. MALLORY:** I am in a prejudiced position. I cannot explain it, however.

**DR. RICHARDSON:** And we could not on the service.

**DR. MALLORY:** One might imagine large tuberculous nodes pressing on the common duct, but I have not seen that in a case of tuberculous peritonitis, and I think it would be unlikely.

#### CLINICAL DIAGNOSES

Recurring biliary infection.

Cholelithiasis, with secondary biliary cirrhosis?

#### DR. ADAMS'S DIAGNOSES

Chronic cholecystitis, with cholelithiasis.

Stone in the common duct.

Ascending biliary-tract infection (cholangitis), with infectious (biliary) cirrhosis of the liver.

## ANATOMICAL DIAGNOSES

Tuberculous peritonitis.  
 Miliary tuberculosis.  
 Pulmonary tuberculosis, healed.  
 Tuberculosis of hilar glands, healed.  
 Cholecystitis, chronic.  
 Cholelithiasis, choledocholithiasis.  
 Nephrosclerosis, moderate.  
 Operative scar, peritoneoscopy.

## PATHOLOGICAL DISCUSSION

DR. MALLORY: This patient continued to pursue a downhill course, and at autopsy we found, besides the tuberculous peritonitis, a gall bladder full of stones, and immensely dilated common bile and hepatic ducts. Twenty-eight stones were counted in the common duct. Gallstones unquestionably were the cause of the jaundice. There was a moderate degree of secondary cholangitis; it was on the border line of chronicity at which one begins to speak of biliary cirrhosis. There were also miliary tubercles in the liver and a great many in the spleen, which was consequently considerably enlarged, and there were scattered tubercles in the lungs. The primary cause of death was the generalized tuberculous infection.

## CASE 28012

## PRESENTATION OF CASE

A twenty-nine-year-old housewife was admitted complaining of headache and diminished vision in both eyes.

She was perfectly well until three years before admission, when her first child was born. Although the delivery was normal, she vomited during the whole course of her pregnancy. At that time, she believed that her blood pressure was normal. After delivery, she had periodic attacks of vomiting, which six months later were accompanied by pains in both sides of the face, over the eyes and at the back of the neck. Vomiting began regularly a week before her period and lasted until the menses began. She was relieved during the time of flow, but vomited again for the following week. The pain lasted twelve hours, whereas the vomiting lasted a week. One year before entry, the patient again became pregnant. Her physician said that her blood pressure was high. During this pregnancy, she vomited constantly, had dizzy spells, and in the seventh month, began having throbbing pain over her entire head, with throbbing in the ears, especially after eating. She miscarried during the seventh month, but the emesis continued, and she lost weight steadily afterward. One month following the miscarriage, the blood pressure was 170 systolic, 120 diastolic, and the

urine showed a heavy trace of albumin. During the next few months, headaches and vomiting continued, and the blood pressure ranged from 200 to 210 systolic, 130 to 140 diastolic. The patient returned to work, but gradually became weak and dyspneic. The menses ceased four months before entry. During these four months, she vomited at least once daily, the vomitus consisting of brown foul-smelling fluid but no blood. During the last three months, she occasionally blew clots of blood from her nose, but had no frank epistaxis; this partially relieved the headache. She also felt more drowsy during this period, objected to having people around her, and finally answered questions in a peculiar manner. One month before admission, she suddenly noticed decreased peripheral vision and could not read well, mainly because of blurring. Three weeks before entry, she was seen in the Out Patient Department. The blood pressure was 210 systolic, 118 diastolic. The urine showed a specific gravity of 1.004, 2 white blood cells and a few epithelial cells per high-power field, and a slight trace of albumin. The red-cell count was 2,900,000 with 50 per cent hemoglobin, and the white-cell count was 12,500. The patient was to return later for study. Two weeks later, constant slight epistaxis began. Three days before entry, muscular twitchings were noted. One day later, the ankles began to swell. She had lost 34 pounds in weight during the previous year.

The past and family histories were noncontributory.

Physical examination showed a well-developed but emaciated, dehydrated young woman, with a pasty, pale appearance, who lay quietly in bed. She was stuporous, answered questions with difficulty and at times did not respond at all. The pupils were normal. The fundi showed tortuous vessels with arteriovenous nicking. The disks were somewhat blurred. Exudate and a small hemorrhage were seen near the macula in the left eye. The tongue was dry and brown, and the mouth covered with sordes. The breath was strongly ammoniacal. Examination of the lungs was negative except for a few coarse rales at the bases. The left border of the heart was 10 cm. to the left of the midline. The apical rate was 140; there were occasional extrasystoles and a marked pulsus alternans, only the stronger beats reaching the wrist. A precordial friction rub was heard. The veins were full but collapsed at the level of the auricle. The liver edge was palpable 3 cm. below the costal margin, and the upper edge was at the sixth interspace. The deep reflexes were sluggish. Occasional muscular twitchings were noted in the extremities.

The temperature was 98°F, the pulse 120, and the respirations 10. The blood pressure was 160 systolic, 90 diastolic.

Examination of the urine showed a specific gravity ranging from 1.004 to 1.014, a large trace of albumin, and 0 red cells, 20 to 30 white cells and many squamous epithelial casts per high-power field. The blood showed a red cell count of 2,600,000 with 50 per cent hemoglobin, and a white cell count of 9200 with 91 per cent polymorphonuclears. The nonprotein nitrogen of the serum was 310 mg per 100 cc, the chlorides 82 milliequiv. per liter, the carbon dioxide combining power 37.2 vol per cent, and the protein 7.6 gm per 100 cc. A lumbar puncture showed normal findings.

The patient rapidly failed and died one day after admission.

#### DIFFERENTIAL DIAGNOSIS

DR ASHTON GRAYBIEL: First of all, I shall briefly discuss and attempt to evaluate certain features of this history that are either of interest in themselves or contribute to the making of a diagnosis.

It would be of help to establish the duration of the illness. The first symptoms, nausea and vomiting, occurred three years before death, during the entire course of the patient's first pregnancy. I am not sure why she vomited—perhaps because of toxemia or neurosis. I believe it is unusual for a patient to have vomiting due to toxemia throughout pregnancy and yet deliver a normal baby—abortion or miscarriage is the rule.

We do not know how long the patient had hypertension before death. She thought that her blood pressure had been normal during her first pregnancy, but she was probably asked the question directly and was not quite sure of the answer. The first definite knowledge of hypertension was near the beginning of the second pregnancy, one year before death. The patient was twenty-eight years of age at that time, which is very young for one to have developed essential hypertension with its sequelae. This immediately arouses the suspicion that the primary disease was in the kidneys. If kidney disease is related entirely or almost entirely to pregnancy, it tends to disappear, and the patient becomes well, once the uterus is emptied. In this case, vomiting continued, and the high blood pressure persisted following miscarriage.

The history states that "during the last three months, she occasionally blew clots of blood from her nose . . . ; this partially relieved the headache." It seems impossible that the loss of such small amounts of blood would be important in this respect.

During the last three months of life, the patient became drowsy and mentally deranged; in the light of later developments, this was obviously due to uremic poisoning. Later, she developed twitchings, whose immediate cause was thought to be disturbances in calcium metabolism.

The urinary findings observed three weeks before death are especially interesting in that there was only a slight trace of albumin and 2 white blood cells and no red blood cells per high power field.

I might point out that the swelling of the ankles noticed three days before death need not necessarily be explained on the basis of heart failure. This swelling may have been due to capillary damage as a result of the high degree of toxemia. The rales heard over the lung bases might be explained on the same basis.

The changes in the retinas and retinal vessels deserve especial note. A small amount of exudate was observed in one eye, the vessels were tortuous, and only one small hemorrhage was seen. In the malignant phase of essential hypertension, the retinal changes are much more marked, and this fact is a strong argument against this diagnosis.

The history states that "there were occasional extrasystoles and a marked pulsus alternans, only the stronger beats reaching the wrist." I have never observed this phenomenon, but in turning to the literature I found that Lewis\* says that it can occur. Nevertheless, I doubt the accuracy of the observation in this case. An electrocardiogram might have shown that the weaker beats were regularly occurring extrasystoles. Without this record, there is some chance for confusion, especially when it is remembered that, in pulsus alternans, the interval between the small and large pulses is shorter than that between the large and small.

A precordial friction rub is not uncommonly heard in uremia. It is due to fibrinous pericarditis and is a grave prognostic sign.

The nonprotein nitrogen was 310 mg per 100 cc, which is an extremely high value. This is final proof of the existence of marked kidney failure. Whenever the nonprotein nitrogen attains the level of 200 mg. or more, it may be safely concluded that the functional capacity of the kidneys is about nil. The low value for chlorides represents chloride depletion as a result of vomiting. The carbon dioxide combining power of 37.2 vol. per cent is proof of acidosis.

If this case is considered in a straightforward fashion, the facts suggest that the patient had developed glomerulonephritis some time in the

\*Lewis, T. *The Mechanism and Graphic Registration of the Heart Beat*. Third edition. 529 pp. London: Shaw and Sons Ltd. 1915. P. 434.

past, and that, at the time of pregnancy, symptoms and signs of kidney failure appeared. During the second pregnancy, she became very toxic. The blood pressure was markedly elevated, probably as a result of the kidney insufficiency. She developed uremia despite the fact that the uterus was emptied, and I think she died with uremic poisoning. There is nothing that would lead one to suspect that the patient had had essential hypertension in the past and died in the malignant stage of the disease. Apparently the heart was somewhat enlarged, but there is no clearcut evidence of congestive failure; the edema over the shins and the rales in the lungs could be satisfactorily explained on the basis of uremic poisoning. The coronary vessels were probably in quite good condition. The microscopic appearance of the myocardium may prove to be abnormal simply because of toxic changes. A curious type of myocarditis associated with uremic poisoning has been described.

DR. PAUL D. WHITE: I quite agree that there probably was not a true *pulsus alternans* in this case but that a bigeminal rhythm due to extrasystoles accounted for the failure of alternate pulse waves to reach the wrist. I have examined a good many cases of *pulsus alternans* and have not found any in which the pulse has actually failed to reach the wrist. However, it does appear that there was marked cardiac enlargement, which is a background for true alternation of the pulse.

Should one expect to find anything wrong with the cerebral blood vessels? It is possible that the patient had edema of the brain or, as so often happens, small hemorrhages. I do not know whether the brain was examined, but I should think that either of these possibilities might be mentioned.

DR. FRANCIS R. DIEUAIDE: I should like to raise the question whether, in spite of the age of this patient, renal damage on a vascular basis should not be considered. It is true she was young, but certain findings suggest the possibility. One is the nature of the urinary findings. If one takes them seriously, the low specific gravity, with the small amount of albumin and relatively insignificant sediment content, seems to me to point toward that type of chronic renal condition rather than chronic nephritis on a previous glomerular basis.

DR. GRAYBIEL: I remain unconvinced that the patient had essential hypertension, which had developed into the malignant stage. Under such conditions, she might well have shown even more abnormality in the urine than she did. If she had nephrosclerosis of fairly short duration, she might well have had many red cells and a great deal of

albumin in the urine. Sometimes, in chronic glomerulonephritis, the urinary findings are not very remarkable. I think that the inconspicuous eye-ground findings are also somewhat against the diagnosis of a severe grade of malignant hypertension. I still favor the diagnosis of a chronic glomerulonephritis, aggravated particularly by the pregnancy.

#### CLINICAL DIAGNOSES

Glomerulonephritis.

Uremia.

Hypertensive heart disease, with congestive failure.

#### DR. GRAYBIEL'S DIAGNOSES

Chronic glomerulonephritis.

Uremia.

Arterial hypertension.

Cardiac hypertrophy, slight to marked.

Uremic pericarditis.

#### ANATOMICAL DIAGNOSES

Chronic glomerulonephritis.

Cardiac hypertrophy, left ventricular.

Pericarditis, acute fibrinous, uremic.

(Uremia.)

#### PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: Very often, at post-mortem, when the kidneys on gross examination are so shrunk that it may be impossible to make a definite diagnosis, even the pathologist has great difficulty in making a decision. In the ordinary type of malignant vascular nephritis in a woman of twenty-nine, the kidneys would not decrease in size to the degree of a chronic glomerulonephritis. The kidneys in a patient with malignant vascular nephritis rarely shrink to less than two thirds the normal weight, in contrast to chronic glomerulonephritis, in which the kidney weight may be less than one fourth the normal.

This patient had chronic glomerulonephritis. The kidneys weighed 90 gm., and microscopically there were innumerable hyalinized glomeruli, with crescent formation, which is characteristic of chronic glomerulonephritis. There was a uremic pericarditis of the so-called "bread-and-butter" type, thick fibrin strands producing interadherence between the two layers of pericardium, and 50 cc. of straw-colored fluid. The heart was hypertrophied and weighed 400 gm. The hypertrophy was for the most part left ventricular and was undoubtedly secondary to the nephritis. There was nothing of significance in the other organs, and no sign of heart failure.



ENROLLMENT FORM FOR PROCUREMENT AND  
ASSIGNMENT SERVICE FOR PHYSICIANS

Dr. Sam F. Seeley, Executive Officer  
Procurement and Assignment Service  
New Social Security Building  
4th and C Streets, S.W.  
Washington, D. C.

Dear Dr. Seeley:

Please enroll my name as a physician ready to give service in the Army or Navy of the United States when needed in the current emergency. I will apply to the Corps Area commander in my area when notified by your office of the desirability of such application.

Signed\_\_\_\_\_

1. Give your name in full, including your full middle name:

2. The date of your birth:

3. The place of your birth:

4. Are you married or single?

5. Have you any children? If so, how many?

6. Do you believe yourself to be physically fit and able to meet the physical standards for the Army and Navy Medical Corps?

7. Have you filled out previously the questionnaire sent to all physicians by the American Medical Association?

8. When and where were you graduated in medicine?

9. In what state are you licensed to practice?

10. Do you now hold any position which might be considered essential to the maintenance of the civilian medical needs of your community? If so, state these appointments:

11. Have you previously applied for entry into the Army or Navy Medical Service? If so, state when, where and with what result (if rejected, state why).

Signature\_\_\_\_\_

Date\_\_\_\_\_ Address\_\_\_\_\_

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established in 1828

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND  
PUBLISHED UNDER THE JURISDICTION OF THE COMMITTEE  
ON PUBLICATIONS

Official Organ of

THE MASSACHUSETTS MEDICAL SOCIETY

and

THE NEW HAMPSHIRE MEDICAL SOCIETY

## EDITORIAL BOARD

Joseph Garland M.D.	Stephen Rushmore M.D.
William B. Breed M.D.	Henry R. Viets M.D.
George R. Minot, M.D.	Robert M. Green M.D.
Frank H. Lahey, M.D.	Charles C. Lund M.D.
Shields Warren M.D.	John F. Fulton M.D.
George L. Tobey Jr., M.D.	A. Warren Stearns M.D.
C. Guy Lane M.D.	Dwight O. Hara M.D.
William A. Rogers M.D.	Chester S. Keefer M.D.

## ASSOCIATE EDITORS

Thomas H. Lannan M.D.	Donald Munro M.D.
Henry Jackson Jr. M.D.	
Walter P. Bowers M.D., EDITOR EMERITUS	
Robert N. Nye M.D., MANAGING EDITOR	
Clara D. Davies, ASSISTANT EDITOR	

SUBSCRIPTION TERMS \$6.00 per year in advance postage paid for the United States Canada \$7.04 per year, Boston funds \$5.52 per year for all foreign countries belonging to the Postal Union

MATERIAL for early publication should be received not later than noon on Friday

THIS JOURNAL does not hold itself responsible for statements made by any contributor

COMMUNICATIONS should be addressed to the *New England Journal of Medicine* 8 Fenway Boston Massachusetts

## A CALL TO SERVICE

WAR has already greatly increased the need of the United States Army and Navy for medical officers, and as pointed out in an editorial in the December 18 issue of the *Journal*, appreciable numbers of medically trained men are required for service in other governmental agencies. Because of this, a meeting of the Procurement and Assignment Service, in conjunction with the medical preparedness committees of the American Medical Association, American Dental Association and American Veterinary Medical Association, was held in Chicago on December 18, to devise means for making available to the Army and Navy the names of all physicians, dentists and veterinarians who are willing to enroll immediately in governmental service. Although this information was

requested on the questionnaires sent out by the American Medical Association, the forms had no official status and were filled out at a time when the United States was not an active participant in the war. Furthermore, the amendment of the Selective Service Act to include all men under forty five years of age places many more physicians in the group of those who may be called for active service.

For the convenience of physicians who are willing to serve the Nation in the event of need, an enrollment form that was carried in the December 27 issue of the *Journal of the American Medical Association* is reproduced on the opposite page. On receipt of the forms by the Procurement and Assignment Service, each enrollee will be classified according to information already available in the national roster of physicians at the headquarters of the American Medical Association, and so far as possible, assignment will be made to the type of service for which he is best suited. It is obvious that adequate medical service to civilian communities, public-health agencies and industrial plants must be continued, and committees are already being established in corps areas, states and counties to ensure the proper distribution of physicians.

To wage war successfully, all groups must be prepared to make great sacrifices, and it is to be expected that the medical profession—trained in a code of selfless devotion to duty—will accept this call to service with the cheerful readiness that it has shown in the past

## BLOOD PROCUREMENT SERVICE

At the request of the Surgeons General of the United States Army and Navy, the American Red Cross and the Division of Medical Sciences of the National Research Council have co-operatively organized a blood procurement service for the purpose of supplying the medical departments of the Army and Navy with human blood plasma. Thus far, six procurement centers are in operation in eastern United States, and five others are in the process of organization. During the past year, sufficient blood has been obtained in Boston to fill



the needs of a pilot plant for the production of crystalline human albumin under the direction of Prof. E. J. Cohn, of the Department of Physical Chemistry, Harvard Medical School.

Now that war has been declared, the activities of the Boston Procurement Center must be tremendously increased to supply blood for conversion to dried plasma, and the prewar quota of 17,000 donors within the next five or six months is but a fraction of what will eventually be needed. Quarters have been established at 691 Boylston Street, a personnel has been trained, and 100 donors are being bled daily. The organization of the procurement center and the technics used are those adopted as standard for the country by the American Red Cross and the National Research Council, and the final product meets all the requirements of the National Institute of Health.

Great care is exercised in selecting the donors. They must be twenty-one to sixty years of age and in good health. They are acceptable only if they have a hemoglobin level of 80 per cent or higher and a systolic blood pressure lying between 100 and 200 and if they have not been bled within eight weeks. Mature minors may be accepted as donors with the written permission of a parent or legal guardian. Five hundred cubic centimeters of blood is taken from donors of average size, and the facts that the repeat donor percentage is high and that reports from employers indicate that mass bleedings at manufacturing plants have not decreased the workers' efficiency indicate that this amount has caused no ill effects.

This meritorious project deserves the wholehearted support of the medical profession, because it not only provides an essential means of saving human life but also affords every citizen an opportunity to make a worth-while contribution to the war effort. A ready response will augment the growing morale of the armed forces and do much to crystallize *esprit de corps* among civilians.

## MEDICAL EPONYM

### LUDWIG'S ANGINA

Wilhelm Friedrich von Ludwig (1790-1865) communicated his vivid description of "a variety

of inflammation of the neck which has recently been of frequent occurrence in this community" to the *Medicinisches Correspondenz-Blatt des württembergischen ärztlichen Vereins* (6: 21, 1836). A portion of the translation follows:

After a series of prodromal symptoms . . . there develops a firm swelling . . . usually in the cellular tissue surrounding the submaxillary gland. This . . . swelling spreads around the neck under the jaw . . . with marked lateral bulging. . . The tongue lies on a floor of . . . indurated bright-red tissue which feels like a hard, calloused ring along the inner border of the jaw inside the mouth. . . Ability to open the mouth is restricted and painful . . . speech is difficult . . . thick and gurgling. . . The skin, . . . in the early stages at least, is very slightly reddened if at all and is normal in texture; . . . later, soft red spots may appear . . . but no pus is ever formed. . . The symptoms of the subsequent rapid course are those of a putrid-typhoid process, and in four to five days, the tenth to twelfth from the onset of the illness, coma develops and death occurs with indications of respiratory paralysis.

R. W. B.

## MASSACHUSETTS MEDICAL SOCIETY

### COMMITTEE ON MATERNAL WELFARE

At the annual meeting of the Council of the Massachusetts Medical Society, held in May, 1941, a resolution to establish a committee on maternal welfare was passed. This resolution also empowered the President to name a committee whose membership should represent geographically the various sections of the State. The resolution was presented to the Council by members of the Section of Obstetrics and Gynecology because it was believed that, to carry on some phases of the work that had come before the section, a committee having delegated authority should be established. In accordance with this vote, the President appointed the following committee: Dr. Judson A. Smith, chairman, Boston; Dr. Thomas Almy, Fall River; Dr. Robert L. DeNormandie, Boston; Dr. M. Luise Diez, Boston; Dr. Christopher J. Duncan, Brookline; Dr. M. Fletcher Eades, Boston; Dr. Arthur F. G. Edgelow, Springfield; Dr. Rachel L. Hardwick, Boston; Dr. Joseph W. O'Connor, Worcester; Dr. Louis E. Phaneuf, Boston; Dr. George M. Shipton, Pittsfield; Dr. Warren R. Sisson, Boston; Dr. Richard M. Smith, Boston; Dr. Raymond S. Titus, Boston; and Dr. Richard J. Williams, Lynn. This committee has met and organized. The chairman, Dr. Judson A. Smith, was appointed by the President; the secretary, Dr. Titus, was elected by the committee.

In October, 1941, a meeting of the Executive Committee of the Section of Obstetrics and Gynecology

cology was held in Boston. It was the opinion of this committee that, since a committee on maternal welfare had been appointed, much of the work that the section had carried on should be relinquished to this committee, an official body of the Massachusetts Medical Society. Hence, the study on maternal welfare, which the Section of Obstetrics and Gynecology has conducted for the past five years, was turned over to the Committee on Maternal Welfare, as of December 31, 1941 and from now on, all work of this type, except that pertaining to arrangements for the annual meeting of the section, will be handled by this committee. The case histories that have been appearing in the *Journal* will continue, at least for the time being. In next week's issue of the *Journal*, a résumé of the study of maternal deaths during 1940 will appear.

#### MEDICAL SOCIAL SERVICE FOR THE HANDICAPPED CHILD\*

In these weekly broadcasts, sponsored by the medical profession you have heard from a great many physicians and public health authorities about the advances in medical knowledge. You have been given information important to every intelligent person, concerning the common diseases and their care.

As one long associated with the medical profession in service to patients I want to share with you some of my experiences as a medical social worker in a large medical institution where specialization in the many branches of medicine is to be found. Medical social service is established in most of our big hospitals and clinics. You may well ask what social service has to do with medical institutions. Any of you who have had experience with sickness yourselves or have had illness in the family know how disturbing sickness can be. Often, it is more than pain and distress. It upsets our regular way of life. It may mean that we must stop work, lose time at school or give up some special pleasure we had anticipated. These experiences are common to us all.

Fortunately not all of us have had the more serious diseases which are well known in our great hospitals and to the medical profession, sicknesses that mean that the patient may not be able to work again or that he must learn to live with a chronic disease that may have to have treatment over a long time. I have in mind a girl with diabetes, who must learn to control her diet habits and who may have to take insulin every day for many years. I think of the boy with infantile paralysis, who must have many months and possibly years of muscle training—possibly operations. He may have to learn to walk with braces. And I think of the child who has lost his precious eyesight.

Does all this bring sad pictures to your minds? If it does I wish you could know as I do many of the courageous cheerful men, women and children who have been able to face such sicknesses, who have done their part in getting well or, if not well, in still finding that life can be very much worth while.

As one such courageous patient said: "It's not what is gone, but what is left for me that counts now. Sometimes sickness and the way the patient takes it are the means of opportunities for a fuller life. It is a curious fact that it may take such experience to awaken us to what we may be. I am thinking of a fine, active young boy, a leader in sports who was stricken with infantile paralysis at fourteen years of age just as he was about to enter high school. For a time, the future seemed very bleak to him. But under skillful medical care and through his own determination to do his exercises regularly he was able after two years to get about with crutches and braces. But this improvement in the condition of his body was only part of this boy's problem. What about his "rager active mind"? What about his education? What can he ever do to support himself? He is not the kind of person who wants to be dependent on others. Herein the medical social worker could help the patient and the doctor. For the doctor, too, wants the patient to be restored to useful living. Accordingly arrangements were made for his education first in a specialized school for handicapped children where the floors are not slippery for crutches and braces and ramps are used instead of stairs. He has made a good record through seven years and with the help of a generous person he is now in college preparing for journalism.

The other day a boy came from a distant town to one of the clinics for examination of his ear. His mother reported that he had been considered dull in school and had to repeat his grade. His parents considered him a "bright enough child but thought he did not pay attention when he was spoken to. Finally, one of his teachers suggested that he was not hearing well and advised the parents to have him examined. At the clinic his hearing was carefully tested and it was found that he heard nothing with the right ear and that the left was defective. For this boy several things can be done. A letter to the teacher advises that he sit in the front row in the right side of the room, so that his left ear can be used as much as possible. Then lip reading instruction can be started so that he may learn to depend on his eyes more than his defective ears for understanding what people say. Periodic examination of his left ear will be made. Let us hope that he has no further loss of hearing. But it will be well to have some aptitude tests to see in what line he has special ability. He should be guided into the kind of work he is fitted for by nature so that his handicap may be minimized.

Perhaps many of you have your own family doctor. If you do you know how much more he does for you than make a diagnosis and order medicine. He is an adviser and friend who helps you face the problems that sickness brings. But in our great clinics where patients go who have no family doctors or our great hospitals to which many people are sent for care it has been found necessary to have a person who can spare the busy doctor's time and give patients counsel in their difficulties and practical help in working out their problem.

Massachusetts like many other states is much concerned about helping people who are in trouble—whether it is support for those who are destitute, protection for neglected children, education of the handicapped, blind or deaf, medical care for crippled children or for the patients with tuberculous cancer and those with mental diseases, rehabilitation of those who can be trained for special work, protection of workers from the hazards in industry, compensation for those injured at work. Then too, through generous citizens there are many privately

\*A Green Girls to Health broadcast given through Station WAAB by Miss Ida M. Cannon on Saturday, November 22, and sponsored by the Public Education Committee of the Massachusetts Medical Society and the Massachusetts Department of Public Health.

supported resources to supplement the public agencies, resources for help in difficult family problems, foster homes for children who cannot be in their own homes, hospitals, clinics, centers for recreation and agencies for helping those who come from across the seas to seek new homes in our land. The medical social worker must be very familiar with all these resources. Her knowledge and skill in helping people to help themselves is called on every day as physicians in our great medical institutions ask her assistance for patients under their care. But if she is a well-trained social worker, she wants every citizen to be self-reliant. She wishes each home to be a center for strength in the family ties, not only when all goes well but also in times of trouble. When she is facing a problem with a patient, it is her purpose to help the patient to help himself, to help the family to meet the problem. Her experience with many similar problems, her knowledge of resources for help when the difficulties cannot be met by the patient and the family alone may be needed. Did you ever notice that when people are not well and things look black, they are inclined to think in circles? They come back to the same place again; it is not real thinking. Worry is a more suitable word for it. Such people need help in straight thinking. They need to have a plan for meeting their problems, whatever they are. It is in this planning how to meet the difficulties that arise with sickness that medical social service may be useful.

Let us take for example the child who is found to have rheumatic heart disease. There are many hundreds of such patients in New England. When the disease is active, the doctor usually tells the patient and his mother that he must stay quietly in bed for weeks, sometimes for months. There may be little or no physical pain for the patient to bear, but he must accept restriction of his activities and loss of school and play that may be more difficult to bear. Medical social service is called on by the doctor to help the mother and patient not only in carrying out the medical orders but also in making a plan with them for a way of life that may have special compensations. To meet the many needs of this family, several services are available. A visiting nurse can teach the mother how to give the child in bed the necessary care, how to keep track of his temperature, how to prepare his food. Massachusetts provides for visiting home teachers to continue education of children who are not able to go to school yet are able to do some homework. If the teacher is not available, there are often people who are willing to act as volunteer tutors for such children. But there is also the question of recreation. Children must be taught to play quiet games, to make things with their hands. Often, the child discovers abilities in modeling, painting or belt weaving that he never knew before. Or in these weeks in bed, he may be led to discover the great privileges we have in our public libraries. Reading may become a new resource for him, not only for information, but for romance and adventure. Through books, he may find that he can travel to far lands and learn of the lives of great men and women of history.

To be really healthy, we must be healthy both in body and mind. We should be making full use of all the capacities God has given us. How few of us do that! Sickness may sometimes be made a real teacher. We discover, for one thing, how precious good health is. But, if we must live with physical limitations, we have freedom to develop our minds, and through use of our latent capacities, we may find compensations for misfortune. This is what many children have taught me. I am grateful to them for their teaching.

## WAR ACTIVITIES

### UNITED STATES ARMY

The following medical officers entered on active duty between November 29 and December 13, 1941:

Wiesner, Ernest E., 1st Lieut., of Brockton, Massachusetts: Camp Edwards, Massachusetts.

Raymond, William H., Jr., 1st Lieut., of Lynn, Massachusetts: Fort Williams, Portland, Maine.

### CIVILIAN DEFENSE

Dr. Augustus Thorndike, owing to the call into active service of General Hospital No. 5, has been obliged to resign from the position of deputy medical director of the Medical Division of the Massachusetts Committee on Public Safety, and Dr. A. William Reggio, of Brookline, has been appointed to the post.

## MISCELLANY

### AIMS OF COLLAPSE THERAPY

The habit of calm appraisal characteristic of English physicians seems to be ruffled neither by the pressure of war emergencies nor by howling bombs. Tuberculosis work in England, although sometimes interrupted, continues to engage the earnest attention of physicians and laymen. American readers will profit by Pearson's clear analysis of the objects of collapse therapy in the treatment of pulmonary tuberculosis (Pearson, S. V. What are we aiming at in collapse therapy? *Tubercle* 22:159-165, 1941), an abstract of which follows:

The objects of treatment in pulmonary tuberculosis are fourfold: to arrest the progress of the disease, to heal the damaged tissues, to restore the general health and working capacity of the patient, and to render his sputum negative. Often, there is likelihood of clash between these objects, and what to do is sometimes overshadowed by the question when to do it. The aims of collapse treatment for pulmonary tuberculosis may be surveyed under eight heads.

*The constitutional effects of this disease are of more importance than the local.* The constitutional symptoms, rather than damage to the lungs, endanger life and health. But the successful treatment of the local lesion is the way to allay the constitutional symptoms. The characteristic feature of the disease, a series of reactions in the connective tissues, only secondarily affects the functions of the breathing apparatus. It is the exudative lesions that produce the most dangerous symptoms, and are most amenable to collapse therapy, although it is not yet known how such therapy affects them.

*Its chief characteristic is that it produces reactions in the connective tissues.* Aside from its effect on gross lesions, including cavities, collapse therapy produces ischemia, passive hyperemia and lymphatic stasis, which encourage proliferation of connective tissues and the production of fibrosis in early lesions. It is well to emphasize this because collapse therapy is too often reserved for the patient with excavation and other gross lesions. The relaxation, the ischemia and the lymphatic stasis affect the diseased parts more than the healthy. But, if the toxemia is lessened, the work of healthy lung tissues is eased because

the function of the latter is interfered with less than it was

*The tubercle bacillus is nearly always "master of ceremonies"* It is a mistake to be apprehensive of secondary organisms within the lesions in the lung, for the tubercle bacillus is the all important etiologic agent. It is time the bogey of mixed infection was laid to rest. The tubercle bacillus is responsible not only for early infiltration of the Asman type (early round foci) or early excavation, but also for liquefaction.

*A re-expanded, healed lung should be the aim of therapy then and as far as possible.* This means that a reversible and temporary type of collapse is to be preferred whenever possible.

*The best induced collapse is always a selective one.* So-called respiratory traumatism" (abnormal stretching of diseased parts) is based on the idea that the movements of respiration do harm to a diseased lung and that collapse treatment counteracts this harm by resting the lung. But on occasion collapse treatment may increase the harm. For example, when a stretched pleural adhesion attached viscally to the region of a cavity in the lung occurs in an artificial pneumothorax. It must ever be an aim of collapse therapy to amend and convert such a condition. The mechanisms that produce harm are those which increase the stretching of diseased parts. These must be discovered with the aid of roentgenograms and even more, by careful observations, on the screen, of respiratory movements. (Slow motion cinematography is being increasingly employed in the study of respiratory movements.)

*Collapse is obtained by relaxing tension of diseased parts.* This has long been emphasized but even now, when movements during breathing and coughing are being studied, too much attention is often given to cavities rather than to the influence of such movements on the relaxation of other pulmonary tissues.

The movements of respiration affect the diseased parts of the lung either directly or indirectly—a distinction not always easy to make. The surrounding parts can be pulmonary or nonpulmonary, and their effect on the tensions within the thorax must be considered. Collapse therapy aims at relieving these and permitting relaxation. Perhaps even more important than expansion, contraction and movement of cavities is the effect of respiratory movements on the lung tissues surrounding and in proximity to a cavity.

*In dealing with cavities, one's aim is, of course, to get rid of them.* Collapse plays a part in this by closing the bronchocavernous passage, stabilizing and reducing intracavitary pressures, starving and debilitating the tubercle bacilli on the cavity walls.

"It always strikes me," says the author, "that the hole in the lung has held far too much of the attention." Efforts to classify cavities have been useful but not inconclusive. One is often in doubt how to interpret an annular shadow. Mistakes are still made between a ring of fibrosis, a zone of reaction around a central focus and one of atelectasis. Even the supposed hole may be found to be no hole on post mortem examination. There are other difficulties. Probably the best classification of cavities is that of Coryllos: open, closed and narrowed.

Early cavities disappear sometimes without any measure to relax anything. When a cavity does not close spontaneously, collapse therapy is used. Artificial pneumothorax would succeed more frequently if the suitable case were found earlier and proceeded with, especially if cauterization of adhesions were more popular. The excavated lung needs relaxation from without, that is by being de-

tached from the bony cage of the thorax, but not under too high a pressure within the cavity itself can keep the hole open, and if such air is absorbed and the compressed lung around the cavity reexpands it will fill the gap. This process is accomplished by getting the bronchial opening blocked and may occur more or less by accident. Cavity closure after an ineffectual pneumothorax occurs fairly frequently, and can be aided by a temporary phrenic operation, but the reason why the cavity closes cannot be explained. Closure may come about through a kinking of the bronchus draining the cavity although a case has been reported in which a kinking had a disastrous effect. One's aim should be to know when a kinking has occurred, when it is benefiting the patient and how it has come about.

Several lessons can be learned for collapse therapy from work with Monaldi's method, namely, the trans pleural decompression treatment of cavities. One of these has to do with the blocking of the cavity. When a cavity becomes blocked, the oxygen is absorbed, and the tubercle bacilli languish. There is good evidence to show that an aim of treatment should be to starve and debilitate the tubercle bacilli on the walls of the cavities. When that has been achieved, it remains for means to be found to allow the pericavernous tissues, either by expansion or in directly by their contractile powers, to close the cavity.

*The prevention of the discharge of the bacilli.* Cavities are the main, if not the only source of the expectorated positive sputum, which augments the danger of bronchogenic spread and spread to other persons. An essential aim of treatment, therefore, is to prevent the discharge of tubercle bacilli. But the restoration of health must come first, a well trained ex-patient who behaves sensibly is not a danger. The restoration of the patient to work must not be forgotten in the desire to eliminate cavities and positive sputum.

Finally, aims should always be based on clinical and x-ray observations, which should not be directed too exclusively to cavities or to the lung condition. Collapse therapy is not purely mechanical. The many factors of the situation must be taken into account. Knowledge of collapse treatment is advancing quickly and modifying medical practice. That is the ever fascinating interest of medicine. As it progresses, certain problems are solved and discussion about them ceases, but new ones arise.—Reprinted, with changes, from *Tuberculous Abstracts*, December, 1941.

## BOOK REVIEWS

*The Political Life of the American Medical Association* By Oliver Garceau 8", cloth, 182 pp., with 14 charts. Cambridge: Harvard University Press, 1941. \$2.50

This curious book is a good example of faulty, arm chair reasoning. Apparently, the author has read widely the official publications of the American Medical Association, including the *Proceedings*, and also many publications of the various state medical journals, to which he gives repeated reference. He has also corresponded, according to his acknowledgment in a preface, with the secretaries of state and county societies, and with Olin West, secretary of the American Medical Association. Apparently, he has never taken the trouble to attend the annual sessions, particularly those of the House of Delegates, nor has he investigated at first hand the numerous activities of the association in its Chicago headquarters. His book, therefore, is decidedly lacking in factual background, and is practically valueless as an authentic or even important contribution to the subject. It would pass unnoticed ex-

cept for the fact that it emanates from the Department of Government, Harvard University, and was published by the Harvard University Press. This, indeed, appears to give it some authority. With this setting, one is surprised to find many statements of doubtful authenticity: paragraphs in which the actual meaning of a situation is twisted to make the author's point, a journalistic style not well fitted to what purports to be a scientific, logical discussion of the subject, and such a biased point of view that it takes away any force that the author might have in argument. This jejune product cannot be recommended as a book worthy of serious study.

*Infantile Paralysis: A symposium delivered at Vanderbilt University, April, 1941. Lecture 1. Poliomyelitis.* 8°, cloth, 239 pp., with 46 illustrations and 2 charts. New York: The National Foundation for Infantile Paralysis, Incorporated, 1941. \$1.25.

In April, 1941, a series of six lectures on poliomyelitis was given at Vanderbilt University under the auspices of the National Foundation for Infantile Paralysis. These lectures have now been published, and since they were given by the leading authorities in this country on various aspects of the disease, the volume presents a report on the current opinions regarding etiology, diagnosis and treatment. The essays are remarkably uniform in both style and scholarship. Because nothing of a similar nature is available in medicine and because of the timeliness as well as the broadness of these contributions, this book is an important contribution to the subject. Great credit should be given to the National Foundation for Infantile Paralysis in arranging these lectures and seeing that they were issued in printed form. The book is excellently printed, with adequate bibliographies and an index. It sells for a fraction of its actual cost.

*Electrocardiography in Practice.* By Ashton Graybiel, M.D., and Paul D. White, M.D. 8°, cloth, 319 pp., with 272 illustrations. Philadelphia and London: W. B. Saunders Company, 1941. \$6.00.

It is becoming increasingly apparent that the electrocardiograph is one of the great achievements of the twentieth century. It makes the heart sign on the dotted line and describe some of its ailments. Yet it is not an instrument on which one may press a button and have the diagnosis appear; nor is it merely a tool of the cardiologist. Rather, like the ophthalmoscope and the microscope, the electrocardiograph is an indispensable instrument in the hands of the clinician. As a result of the research that has been done, an extensive literature has accumulated on the subject. The practicing physician whose interest in cardiology has been aroused and who wishes to make the electrocardiograph part of his armamentarium finds himself in a daze. The periodic literature on electrocardiography is vast and scattered, and it is impossible for the novice to get a clear conception of the subject. Nor does the average book on cardiology cover the subject of electrocardiography sufficiently. On the other hand, some of the best books on electrocardiography are cumbersome, because of the amount of space given to the technical principles involved.

This book seems to be an answer to many a physician's prayer. It is a practical book on electrocardiography, unfettered by needless theory. The authors have eliminated the detailed descriptions of the various types of electrocardiograms, the details of technic and the underlying physiologic principles involved. After a brief introduction, the book deals with the interpretation of

electrocardiograms, normal as well as abnormal. As the authors have rightly stated, "Errors in electrocardiographic interpretation are probably more often made by calling normal variations abnormalities, than by missing real abnormalities when they are present." The authors give records of all types of variations from the normal. Practically every heart disorder is represented, including such factors as drugs that affect the electrocardiogram, or such miscellaneous conditions as anemia and trauma. Each record is printed on the right side of the book, and a short history of the patient, with an interpretation of the picture, is given on the opposite side. This is as it should be: the electrocardiogram is part of the entire clinical picture. The second part of the book is devoted to electrocardiograms for interpretation. These are records without labels, on which the physician can test himself. It is an excellent source of self-instruction. One can check himself by reading the interpretation and the history on the opposite page. Among textbooks on electrocardiography, the book stands out as one of the most practical and comprehensive. It is a valuable addition to any clinician's library.

*The Doctor Takes a Holiday: An autobiographical fragment.* By Mary McKibben-Harper, M.D. 8°, cloth, 349 pp., with 17 illustrations. Cedar Rapids, Iowa: The Torch Press, 1941. \$2.50.

Dr. McKibbin-Harper, well known for her previous travel books and for her close association with the work of the American Medical Women's Association, describes in this book her many travels to Europe and to the Orient. Her chief interest was naturally in medical conventions in which women played a prominent part, and in visits to women physicians in various parts of the world. In this book, one finds much material of value, and it is indeed a record of extensive travels by one who had an appreciative mind and who could evaluate conditions, particularly in the Orient. The illustrations are of considerable importance, since they show pictures of medical scenes, hospitals and doctors rarely found in other medical books. The volume is rather poorly printed, and there are numerous minor errors that should have been corrected. In general, it is a fairly interesting travel book by a physician.

*Clinical Aspects of the Electrocardiogram, Including the Cardiac Arrhythmias.* By Harold E. B. Pardee, M.D. Fourth edition, revised. 8°, cloth, with 219 illustrations and 14 tables. New York: Paul B. Hoeber, Incorporated, 1941. \$5.75.

The fourth edition of this popular text maintains the high standard set by its predecessors. In the eight years that have elapsed since the previous edition, new developments in the field of electrocardiography have taken place at such a rapid pace that it has been necessary practically to rewrite the whole book. In particular during this period, various thoracic leads have established their usefulness in practice, and perhaps the most important new feature is the consideration given to the precordial leads in persons with normal and with diseased hearts. The bibliography that accompanies each chapter has been selected with discrimination, and furnishes in itself a valuable guide to anyone wishing to go deeper into the subject. The book is thoroughly practical in its orientation and is presented in such a way as to be useful even to the beginner in the field.

(Notices on page x)

# The New England Journal of Medicine

Copyright 1942 by the Massachusetts Medical Society

VOLUME 226

JANUARY 8, 1942

NUMBER 2

## MIDDLESEX SOUTH AND MASSACHUSETTS MEDICINE\*

HAROLD G GIDDINGS, MD †

NEWTON CENTRE, MASSACHUSETTS

IN the brief time allotted for the delivery of this address, it is quite impossible to do more than touch in a most general way on a few of the highlights in the ninety-one years of vigorous and progressive service of the Middlesex South District Medical Society, not only to the medical profession itself, but also to the twenty six communities that are the society's component parts. From its beginning, as a unit of the Massachusetts Medical Society, as well as from earliest Colonial days, the society has always had within its ranks a group of able, progressive, vigorous and unselfish men, and in what follows an attempt has been made to describe some of the contributions that our district has made toward the advance of medicine in Massachusetts.

Following authorization by the Council of the state society, October 2, 1850, "A meeting of the Massachusetts Medical Society, residing in some thirty towns in the south part of Middlesex County, was held at Waltham on the twentieth of February [1851] to form a district medical society. The following gentlemen were chosen officers: Dr Josiah Bartlett, of Concord, president, Dr Jonathan W Bemis of Charlestown, secretary, and, Dr Edward Warren, of Waltham, treasurer."

After printing this notice in its issue of March 5, 1851, the *Boston Medical and Surgical Journal*, possibly imploringly, remarked "For the above information we are indebted to the *Daily Times* of this city. When will our medical friends learn to send such intelligence to the medical press?"

The establishment from time to time of district societies was part of the natural growth of the state society, which had come spontaneously into being in 1781. As the population of the state increased, and as new communities sprang up or older ones expanded, it was a natural sequence

that the physicians in these communities should associate themselves together in local and in district societies, for there they could enjoy the advantages of social contact, report and discuss their interesting and problem cases, the worth or worthlessness of different modes of treatment, and bring to the attention of their fellows any new discoveries that might be of value.

One subject, however, seems to have been taboo, if one may judge from excerpts taken from an address by Dr Joseph Reynolds, of Concord, at the semiannual meeting held at Waltham, November 1, 1854. Certain portions of this address are interesting, for they convey some idea of the intense feeling that existed against the homeopaths.

One subject, we trust, will be entirely ignored, unless forced upon one's attentions by inexorable fate we mean quackery. The profession have wasted enough of their strength upon this already. It is of no use to be eternally complaining that quacks abound, that people will employ them, that homeopathy is spreading in a particular district, and that some of its professors will persist in retaining their connection with our medical societies. The only way to put quackery down is to raise the standard of medical education, and thus keep all quackery *outside* of the profession where it will do no great harm. Towards accomplishing this result the members of each district society, individually and collectively, should contribute their position.

Incidentally, at about this time, the parent society was concerning itself with a study of homeopathy and its tenets, with no less a committee than Drs George Hayward, J B S Jackson and Oliver Wendell Holmes. The following resolution was accepted and passed: "That a diploma from a homeopathic institution shall not be received as an evidence of medical education, [and that] attendance at the lectures at such institutions [shall not] be regarded as qualification to entitle candidates to an examination for license from the society."

\*The Annual Orator delivered before the Middlesex South District Medical Society Cambridge May 14 1941

†Vice president Middlesex South District Medical Society

In the act of the legislature of November 1, 1781, by which the state society received its charter, no provision was made for the forming of local or district societies that should become integral parts of the parent society. In fact, the membership was limited to not more than seventy, nor less than ten, fellows, eleven constituting a quorum. In three years, however, it became evident that there was need for subsidiary committees, and a vote was taken in Mr. Furnass's room in Court Street on Wednesday, October 26, 1785, which provided for the "appointment of corresponding committees" in the several counties of the Commonwealth. These committees were designed to encourage meetings of physicians in their respective counties and the reporting of unusual or important cases, either verbally or by correspondence. Accordingly, committees were appointed for the following counties: Suffolk, Essex, Middlesex, Worcester, Hampshire, Berkshire, Bristol and Plymouth, Barnstable, Dukes and Nantucket, and Lincoln and Cumberland—for Maine was a part of Massachusetts until 1820. The first reference in the state society records to a report from the Middlesex Committee was under date of April 8, 1789. The entry reads as follows:

The corresponding committee of Middlesex reported and laid on the table a copy of the Middlesex Medical Association.

This report, signed by Isaac Rand and Oliver Prescott, addressed to Dr. N. Appleton, recording secretary, was dated April 3, 1789, and read: The committee appointed for the County of Middlesex report the enclosed printed regulations of an association of physicians, as the best means they could devise for promoting the views of the Medical Society in the county they belong to.

The printed document, which is headed "Middlesex Medical Association," is two and a half quarto pages in length, and contains ten preambles and a set of bylaws consisting of twenty articles. Despite this excellent beginning, it is impossible to trace this Middlesex Association further.

The records of the state society contain no further reference to a Middlesex association until 1844, although the *Historical Contributions of Lowell, Massachusetts* mention the fact that the first county medical association was founded in 1829, but was disbanded in 1833. Another society, which began in 1839, was merged into the Middlesex North District Medical Society in 1844.

In 1803, the legislature removed the restriction limiting membership and provided machinery for the formation of district societies. The first application was from a group of Boston men, who requested that their society be allowed to include

the "fellows residing in the neighboring towns of Charlestown, Cambridge and Roxbury." This petition was granted by the Council on February 2, 1804, but strangely enough, no further record of this group is to be found.

To obtain a proper perspective of the development of the district societies, it may be well at this point very briefly to review, in chronological order, the admission of these various units to the state society, and to note, in passing, that Middlesex South was one of the very last to become an entity. The order of admission was as follows: Worcester, 1804; Essex South, 1804 or 1805—the exact date is not given; Berkshire, 1807—although the petition for admission was granted, this society apparently never functioned, and another petition was granted in 1818, regular meetings beginning on July 1, 1819, and the charter being accepted by the state society on May 4, 1820; Hampshire, 1831; Bristol South, 1839; Barnstable and Hampden, 1840; Essex North, 1841; Middlesex North, 1844; and Suffolk and Bristol, 1849. The group consisting of Middlesex East, Middlesex South, Norfolk and Plymouth came into existence in 1850, as Franklin did in 1851, by redistricting and by petition. Worcester North was established on petition in 1858, and Norfolk South was admitted in 1884. Except for a few boundary adjustments, there have been no changes or additions in the last fifty-six years. One sometimes wonders why Charlestown and Brighton, parts of Boston, should be included in the Middlesex South, instead of in the Suffolk, District. The explanation is that, as territory surrounding Boston merged with the city, these districts became a part of Suffolk County. Charlestown, however, remained in the Middlesex South District, as Brighton, previously set off from Cambridge, did when it became part of Boston in 1874.

Of the many physicians in the history of the Middlesex South District Medical Society, some naturally attained more prominence than the majority of their fellows. In his delightful address, entitled "The Heritage of Middlesex South," which he delivered at our annual meeting in April, 1927, Dr. Dwight O'Hara reviewed in some detail the attainments and personalities of several of the more interesting of these earlier members. Because certain of them were so outstanding and so obviously influenced the course of medical thought and progress,—although their contributions were made before Middlesex South became an entity,—it seems proper again to speak of them here. One is impressed by the frequent occurrence, even in early Colonial days, of names with which we of recent times are familiar, and

which we instinctively associate with the best in medicine.

The name "Tufts" occupies a place of high honor in the state society's records. Simon, the elder, practiced in Medford from 1725, where he served as preceptor to General John Thomas, of Dorchester Heights fame. He was the father of Simon Tufts, the younger, who succeeded to his father's practice in 1746, and of Cotton Tufts, of Weymouth, who became one of the prominent founders of the Massachusetts Medical Society. Simon, the younger, although not a founder of the state society, early became interested in its affairs. He had a hand in designing the seal (1782), was a member of the first auditing and budgeting committees (1783), and was among the first to present a paper before the Society (1784).

John Brooks, also of Medford, studied with Simon Tufts, Jr. He served at Lexington and Concord and, later, in New York, rising to the rank of adjutant-general. He was an ardent supporter of Washington. After the war, he resumed practice in Medford with his old teacher, but became interested in politics, and in 1816 was elected governor of Massachusetts. He subsequently resumed practice and was president of the Massachusetts Medical Society from 1823 to 1825.

Dr. William Kneeland, of Cambridge, served from 1784 to 1786 as second president of the newly formed Massachusetts Medical Society. He was the first of a goodly number of Middlesex South men to be thus honored. Dr. Kneeland was one of a committee from the state society to attend the induction into office on October 7, 1783, of the newly appointed professors of the "Medical Institutions of Harvard University"—a very solemn occasion in Cambridge Meeting-House. As the state society and medical school had started at about the same time, the question of which should have charge of licensing prospective practitioners soon arose. Dr. Kneeland, as one of a committee representing the Society, had an active part in negotiating the matter, which was not definitely settled until 1793. With Simon Tufts, the younger, he also helped in the first audit of the Society's finances, and in preparation of the first budget.

Another example of father and son, both beloved physicians who influenced medical thought in this district, was that of the two Josiah Bartletts—the elder of whom, born in 1759, practiced in Charlestown, and the younger in Concord. Josiah, of Charlestown, was prominent in the reorganization proceedings of the state society in 1803, helping to draft and present the petition to the General Court for these changes. He also

took part in writing the new bylaws and served on committees concerned with the formation of a district society in Boston,—“to include Roxbury, Charlestown, and Cambridge,”—both in 1804 and 1809, neither of which efforts succeeded. In 1810, he delivered the annual dissertation, entitled “On the Progress of Medical Science in Massachusetts,” which was regarded as “a noteworthy paper” and in which he pointed out the stimulus that the Revolution had given to medical investigation, the advantages of the army hospital department to students in medicine, and the fact that Washington had instituted in this state the first medical examinations for candidates for practice. Two years later, in 1812, he urged that the communications of the society be published in the *New England Journal of Medicine and Surgery*, which was just starting, as the official organ of the Massachusetts Medical College, with the professors of the school as its editors, in 1813, he suggested that a committee of the state society be appointed to confer with the professors of the Harvard Medical School on the best method of arranging a uniform plan of medical education.

Marshall Spring, of Watertown, had the doubtful distinction of being the first fellow to have been disciplined by the Massachusetts Medical Society. He had joined in 1784, and at the meeting of the Council on November 5, 1788, a letter was presented by Dr. James Lloyd, an outstanding physician in Boston, accusing Dr. Spring “for conducting in an improper manner as a fellow of this Society.” The censors, Drs. Joseph Gardner, Isaac Rand, Jr., and Lloyd had “after a fair impartial hearing adjudged a pupil of Dr. Spring’s as not qualified for present admission to practice.” According to the charge, Dr. Spring had criticized the censors and taken exceptions to their ruling, and “in a most injurious manner declared his opinion that this pupil was rejected through the influence of the subscriber [Dr. Lloyd] to gratify a personal pique and animosity.” Consideration of the charges was postponed from one meeting to another, until in the presence of both accuser and accused, on June 2, 1790, the Council “voted—that all records that have been made respecting the controversy . . . be considered as expunged and done away with.”

Early in his career,—he graduated from Harvard in 1762,—Dr. Spring built up a large practice in Watertown and the neighboring territory. Although a Tory in affiliations and convictions, he was among the first to arrive at the Battle of Lexington, where he gave freely of his skill. Iconoclastic in his outlook, he seems to have enjoyed the confidence of his community and to have had



many traits that endeared him to his followers. He died in 1818, at the age of seventy-six.

To have been chosen the first professor of theory and practice of physic in the Harvard Medical School, as Dr. Benjamin Waterhouse, of Newport, was in 1782, at the age of twenty-nine, is sufficient reason for his inclusion here; in addition, his introduction of Jennerian vaccination into this country in 1800 by courageously inoculating his six children with cowpox vaccine, and subsequently with smallpox, assures him a high place among our illustrious predecessors. The knowledge that he took but little interest in the actual practice of medicine, and that he "seemed always happiest when in opposition," cannot detract from the distinction of having been the instigator of a great forward step in American medicine. He died in Cambridge in 1846.

Among the more than two hundred delegates to attend the first meeting of the American Medical Association, which was held at Philadelphia in May, 1847, was a group of thirteen from Massachusetts. These gentlemen returned obviously much impressed by what they had seen and heard, and advised hearty co-operation in carrying out the measures proposed at the convention, which, they said, "would promote the welfare of the community and elevate the character of the medical profession." Resolutions were passed by the Council to the effect that it approved the formation of a national society, that delegates be appointed to attend its next meeting, and that a committee be named to determine the number of delegates to which the Society was entitled and to nominate a list of them. It is a matter of pleasant record that the Middlesex South District Medical Society had a part in establishing the agreeable relation between the national and the state associations. This was through the appointment of Josiah Bartlett, of Concord, on the above committee.

Dr. Bartlett was the first district president, having been elected on February 20, 1851. Like his father, Josiah, of Charlestown, he was a man of positive character, who enjoyed a very large practice. In fact, that of his father and his own, overlapping one another, covered a complete century. He was a councilor for many years. As president of the state society (1862-1864), he presided over one of the few annual meetings to be held, up to this time, outside Boston, that is, at the Berkshire Medical College in Pittsfield. His chief constructive interest, as president, was in furthering the efforts of his friend Dr. Henry I. Bowditch to establish a state board of health and vital statistics, but because the Commonwealth

was busily engaged in war activities, the effort came to naught at this time.

Very shortly after establishment of the Middlesex South District and the organization of its medical society under Dr. Bartlett, its members took an active and influential part in the proceedings of the Council. Of course, many of the gentlemen who had previously been admitted to the state society were merely reclassified, and it was natural that the names of some of them should have appeared before, as well as after, the redistricting of 1850. Prominent among these members was Dr. Morrill Wyman, one of the most revered, best loved and illustrious of all Massachusetts physicians. During his long and fruitful life, which covered ninety-five years, medicine was the one object to which he bent all his energies. "Practitioner, student, investigator, at no period of his life, even to the end, did he cease to be interested in the great discoveries which, in his generation, added so much to the science of medicine." Since his character and attributes have been so well described by others, and since so many anecdotes have been told about him, merely a brief summary of his doings as a member of the state and district societies is presented.

The first mention of his participation in these activities was in connection with a vote by the Council, on February 20, 1848, authorizing the appointment of a committee of five to make plans for the next annual meeting, because it had become evident that the details involved in this undertaking required the services of a small, compact group. Dr. Wyman, as a member of this first Committee of Arrangements thus helped to inaugurate an important custom, which has been followed for ninety-two years and has contributed much to the pleasure and efficiency of the annual meetings of the state society. In 1850, or thereabouts, he devised the cannula and trocar used by Dr. Henry I. Bowditch in performing, on April 17, 1850, the first thoracentesis done in this country. In April, 1855, Dr. Wyman attended the annual district meeting as councilor; in 1856, he was elected vice-president and gave the annual address, "On Intestinal Obstruction, with Especial Reference to the Treatment"; in 1857, he was re-elected vice-president, and in 1864, he was elected censor.

At the annual meeting of the state society, held in Pittsfield in 1863, Dr. Wyman gave the annual discourse, "The Reality and Certainty of Medicine." In 1866, he read another paper at the first two-day meeting of the Society ever held.

By 1868, physicians throughout the state had become concerned with the malodorous conditions

surrounding the office of coroner. In February of that year, the Council directed the naming of a committee to "request of the Governor and his council, the appointment, when practicable, of medical men to the office of coroner, in the different districts of this state." The conditions leading up to this request are discussed later. Dr. Wyman was put on this important committee, which, the following October, reported back to the Council that it had seen the governor, Alexander H. Bullock, and had been assured by him that the Council's resolution would be considered, whenever there was a vacancy in the office of coroner. Although no immediate change was made in the system, the matter had been brought into the open, and the way paved for the abolishment, nine years later, of an antiquated, inefficient and corrupt system.

The library of the Massachusetts Medical Society, in the course of its ninety years' existence, passed through various vicissitudes. Provisions were made for it in the first bylaws of the Society, adopted April 17, 1782, and regulations put in force that today would be regarded as Hitlerian in severity. The library, apparently, was never very flourishing, never had many volumes, and was relatively little used. When the librarian reported, in 1871, that no one had consulted the books during the previous year, it was proposed that the published volumes of the society be sold to members at twenty cents a volume, and that the remaining books be deposited in some public library. Fortunately, the Boston Public Library became the repository of most of them. After this provision had been carried out, however, there still remained in the society library several copies of *Medical Communications* and other volumes. The priceless value of these books, manuscripts and records was recognized and stressed by Dr. Henry I. Bowditch, Dr. Morrill Wyman and others, with the result that in February, 1874, the care of this material was entrusted to them and to Dr. Francis Minot, as a special committee which in turn, and as a happy sequel, stimulated Dr. James R. Chadwick to found the Boston Medical Library in 1875.

The Cambridge Hospital was incorporated in 1871, but remained open only a year because of a lack of funds and interest. In 1874, as president of the corporation, Dr. Wyman headed a committee to raise money. He had grave doubts of the success of the venture, because of the services being rendered by the Massachusetts General Hospital to Cambridge, as well as to Boston, but he accepted and, as Rev. Dr. Francis G. Peabody said at the dedication of the Morrill Wyman

House on October 29, 1929, "brought to the task all that energy and intelligence which he always so freely placed at the service of his fellow citizens."

When the hospital was dedicated, on April 29, 1886, Dr. Wyman, still president, gave the address. He continued in this office until 1892. His last official act as a councilor was at the October meeting in 1902, when at the advanced age of ninety, but still keenly aware of values, he introduced a motion that an index be made of the *Medical Communications* of the Society, which had been published since 1790. The forty-page pamphlet, issued the next year, indexed both authors and subjects and has saved much time and labor to those interested in the catalogued material. Morrill Wyman House, in its quiet setting by the Charles, is indeed a fitting memorial to the beloved physician whom it honors.

Reference has already been made to the archaic and inefficient coroner system that was in operation in the State until 1877, when it was replaced by the present, and much more satisfactory, medical examiner system. Its origin, workings and inadequacies, and the contrasting efficiency of the medical-examiner system have been described by Dr. Timothy Leary, as follows:

The coroner is of purely English derivation, and the system was inherited by us from our Anglo-Saxon forebears. "The office of Coroner is of so great antiquity that its commencement is not known."

The first formal statute after Magna Charta dealing with the Coroner is that of Edward the Confessor [sic] in the year 1276. His duties were, with others, "to take a View of the Body and the Wounds and the Cuts [and by inquiring] whether the Killing was by Felony or Misadventure of the Manner of the Killing, with what Weapon, and all of the Circumstance."

With the passage of time his duties were largely limited to determining the cause and manner of death, where death was supposed to be due to violence, and to cataloguing and evaluating property, which was dead and [gift of God], or forfeited in connection with a violent death. . . .

In the early days in England the office of coroner could be held only by 'lawful and discreet knights.' In modern times the appointees, both in England and here, have often owed their preference to office to political favor and the results have been sometimes unfortunate. In Massachusetts, coroners were appointed by the governor and council and no limitation was placed on their number. On petition to the governor and council, any citizen, if he met with their approval, could become a coroner. The result of this procedure in the county of Suffolk was a series of scandals, through the appointment of unfit men, which culminated in 1877 and led to joint action by the profession and the bar, . . . for the reform of the evil

As pointed out by Theodore H. Tyndale, a lawyer who represented the bar:

London with its enormous population, had four coroners; New York with a population three times that of Boston had four, with one medical deputy each; Brooklyn, with a population one third to one half greater, had two; Philadelphia, New Orleans, and Chicago, *two* each; San Francisco, Baltimore, Washington, and Cincinnati but *one* each—a total of twenty-four for all these large cities taken together.

Suffolk County, consisting chiefly of Boston, had forty-seven coroners, . . . almost twice as many as all the above named cities combined; of the forty-three coroners in Boston, thirty-one were regular physicians and members of the Massachusetts Medical Society, two were registered as members of the Massachusetts "Eclectic Medical Society," seven were what were known as "other physicians," while four were non-professional gentlemen. Of these last, one was an auctioneer, another an insurance agent and broker, a third vended patent medicines, while the fourth figures simply as "notary public and coroner."

Facing this situation, in October, 1876, the Council voted that the President appoint a committee of five "to take into consideration the defects of the present laws relative to the appointment and practices of coroners, so far as these defects involve the Medical Profession, and to report . . . what action, if any, is advisable." The committee named consisted of an unusually strong group—Benjamin E. Cotting, J. C. How, W. L. Richardson, J. Collins Warren and William W. Wellington, of Cambridgeport. That they gave very earnest and thoughtful consideration to their problem, working in conjunction with Mr. Tynedale, is evidenced by the searching report they submitted to the Council on February 7, 1877. This report, too lengthy to be presented in detail, was well summarized by an editorial in the *Boston Medical and Surgical Journal*, which stated that:

. . . The [coroner] system is a remnant of past and obsolete usages, and is wholly unsuited to the needs of the present times; that the powers pertaining to the office of coroner are many, unrestricted, and dangerous, and that perversion of them is already notorious, the manner in which inquests are conducted being too frequently objectionable; that the number of coroners possible under the law is unlimited, and at present the appointments are far too numerous and easily obtained, many of those now holding office being totally unfit for the place, and the deeds of some being scandalous; that no redress is practicable, except through a very tedious process, "an address of both houses of the legislature to the governor," one too complicated ever to be resorted to; that the system is a very expensive one and "even when an inquest is unexceptionably made, it is absolutely useless as an aid to justice, and what is still worse, may in fact favor the escape of the guilty."

The report itself ended with the recommendation that the president name a committee of five to cooperate with committees of other interested associations, or persons, to present the matter to the legislature, and to seek reform. The same com-

mittee was appointed as before, with the addition of Dr. William Cogswell, of Bradford, president of the Society, as chairman. So energetically did they perform their task, working in conjunction with other interested groups, that on May 9, 1877, the governor signed the present Medical Examiner Act, entitled "An act to abolish the office of coroner and to provide for medical examinations and inquests in cases of death by violence." This act has stood the test of sixty-four years, and has always operated for the interests of the public.

That the members of the Middlesex South District Medical Society had long been concerned with the inadequacies and abuses of the old system is evidenced by occasional entries in the records. In April, 1864, those attending the meeting expressed pleasure that Dr. Francis H. Brown, of Cambridge, had been appointed coroner for the county and "trusted that this was the beginning of a change which would extend throughout the whole Commonwealth, until every district should be represented by a medical officer as active and competent as this gentleman." And again, in 1869, "The subject of autopsies ordered by coroners and the collection of the established fees was introduced. After an animated discussion, a committee of three was appointed to wait upon the County Commissioners and to discuss the subject with them with a view to establishing a basis for future action in such cases." Because of this interest, it was but natural that when the matter came to a head in the state society, the president should have chosen a representative from Middlesex and one who had been active in affairs of the district, Dr. William W. Wellington, of Cambridgeport. Dr. Wellington graduated from Harvard in 1832, and practiced in Cambridgeport all his life. His father had for a long period commanded the principal practice in the whole northern district of Cambridge. Dr. Wellington is described as a scholar, as an outstanding physician, and as taking an active interest in public, as well as in professional, affairs. He was, for example, for many years secretary of the Cambridge School Committee; in fact, he was sometimes referred to as "The Committee." During the two decades 1850 to 1870, his name constantly appears in the district society's records: as one of the first secretaries, as counselor, as vice-president, and in 1862, as president. For several years after that, he served as commissioner of trials. He gave the annual address before the state society in 1870, and the next year became one of the incorporators of the Cambridge Hospital. Dr. Wellington was among those who opposed admission of women to the state or district societies. This matter first arose in June,

1867, when the trustees of the Massachusetts General Hospital requested an opinion from the Council concerning the expediency of admitting female students to visit its wards. The vote of the Council, forty nine to seven against, left no doubt where it stood; and, for good measure, it also disapproved the admission of "females" to medical schools. Dr. Burrage suggests that the use of the word "female" in this instance represents a possible belief in Kipling's dictum that "the female of the species is more deadly than the male."

In October, 1872, Miss Susan Dimock, a native of North Carolina, applied for admission to the state society. She had, in 1866-1867, studied medicine at the New England Hospital for Women and Children in Roxbury, but because no medical school here would admit her, had gone to Switzerland, where she graduated from the University of Zurich in 1871. Returning to Boston, she became head of the above mentioned hospital, and in 1872 established the first training school for nurses in the United States. Dimock Street, Roxbury, was named for her. The question of Miss Dimock's eligibility was referred to a committee, of which Dr. Wellington was a member. The majority recommended that she be allowed to take the examination, but at Dr. Wellington's suggestion the matter was referred to legal counsel for guidance. On the advice thus obtained, "the committee reported in 1873, that in their opinion the society had the power to admit, or refuse to admit, females to membership," whereupon the Council voted that the censors be instructed not to admit them.

There the matter rested until June, 1875, when another committee was appointed to report whether some plan might be devised whereby women thoroughly educated in medicine and surgery might receive the rights and privileges of fellowship. This committee's report in October still showed a division of opinion, and Dr. Wellington's motion on behalf of the minority, recommending indefinite postponement, was adopted, after rather lively discussion.

The next move came as a result of resolutions passed in October, 1877, by the Middlesex South District Medical Society and presented to the Council in June, 1878. These resolutions favored granting women the privilege of examination and admitting to fellowship those properly qualified. This vote suggests that there must have been many members in his district who disagreed with Dr. Wellington's stand. No action was taken on the recommendation of the Middlesex group, however, until June, 1879. Meanwhile, a questionnaire had been sent to all members of the state

society, to obtain a general expression of sentiment in regard to admitting women to fellowship. Of the replies received, 71 per cent favored some form of recognition, and 28 per cent were opposed to any action whatsoever. The committee appointed by the president in June, 1879, to consider the Middlesex South resolutions presented, the following October, as seemed to have become customary, both majority and minority reports. Signing the former was Dr. Alfred Hosmer, of Watertown. The minority report, however, instructing the censors to admit women for examination was the one finally adopted. But despite this vote, many objections were raised, and through a series of parliamentary maneuvers, final settlement was delayed to June, 1882. At this time, after a struggle of fifteen years, the society voted to grant to properly qualified women the same privileges as to men.

In 1869, the legislature, after many requests from the state society, created a board of health, the first to be established in the United States. So efficiently did it operate, under the chairmanship of Dr. Henry I. Bowditch, that it served as a model for the rest of the country. Because it was so influential, a brief review of the events leading up to its establishment may be of interest.

Agitation for recognition of, and action regarding, public-health problems began in 1839-1840, with the report of a committee to the Council pointing out the necessity of correctly reporting all births, deaths and marriages. An act passed by the legislature in 1842, although apparently not so far reaching as the committee wished, "at least prepared the way for a more perfect system hereafter." On May 2, 1849, the legislature, at the instance of the American Statistical Society, seconded by the Massachusetts Medical Society, authorized the appointment of a committee to make a sanitary survey of the State. The commission, made up of laymen, sought and received assistance from the Council, especially regarding nomenclature of diseases and causes of death. The report of this committee, published in 1850 and spoken of as "a remarkable document," subsequently became the basis of all future health legislation. In 1857, it was proposed that each fellow make, to the secretary of his district society, an annual return on a common form of his cases of the preceding year, this report was to be abstracted and delivered to the secretary of the parent society. Because reports were received from about only one sixth of the men in active practice, the plan was modified the next year so as to provide for the registration of only "zymotic diseases," now

known as contagious diseases. These reports, covering the years 1857 and 1858, appear in the *Annual Transactions* for 1860.

In February, 1861, the state society seconded the petition of the Boston Sanitary Association to the legislature, for the establishment of a state board of health, which should have charge of "the sanitary interests of the people," and the registration of births, marriages and deaths. Anson Hooker, of Cambridge, active for many years in Middlesex South affairs, was a member of the committee representing the Massachusetts Medical Society. The legislature disregarded this petition, as it did others submitted in each of the next two years, for the "establishment of a state sanitary commission." Despite these rebuffs, however, the Society continued its pressure year after year, until finally in 1869 the legislature succumbed, and as already pointed out, set up the first board of health to be established in the United States. This board, working in conjunction with the state society, immediately became an active influence in bettering health conditions. It continued to operate as an entity until 1879, when the legislature, against the vigorous objections of Dr. Bowditch and rather shortsightedly, merged it with the State Board of Health, Lunacy and Charity. Dr. Bowditch resigned in protest, and a year later Dr. Henry Pickering Walcott, of Cambridge, was chosen health-officer. He filled this position until 1884, when he was made chairman of the Section on Health. Apparently realizing its earlier mistake, the legislature in 1886 separated the health department from the others, making Dr. Walcott its chairman. Under his able guidance, and that of the secretary, Dr. Samuel Abbott, of Wakefield, the board made great advances and became noted throughout the country. Dr. Walcott resigned in 1914, after a distinguished service of thirty-four years, when the old board became the present Department of Public Health.

That Dr. Walcott was essentially an administrator is attested by the many public offices he held. An austere and dignified presiding officer, he served for many years as chairman of the Metropolitan Water and Sewage Board, as chairman of the trustees of the Massachusetts General Hospital, as overseer, and in 1900 and in 1905, as acting president of Harvard College. He was the state society's orator in 1889, and its president from 1896 to 1898. During his term, the censors' examination of candidates in November and May was established. He and Dr. W. W. Wellington were the only physicians among the seven incorporators of the Cambridge Hospital, and in 1892, Dr. Walcott succeeded Dr. Morrill Wyman

as president of its trustees, serving until 1917. He will long be remembered as a gentleman who brought great honor to his district and state societies and remarkable administrative ability to the many positions of trust he was called on to fill.

To have served as councilor for approximately fifty years, and never to have missed an annual meeting in a long lifetime, is a rare distinction. Such was the record of Dr. Edmund H. Stevens, of Cambridge, who was a familiar figure to most of us up to the time of his death, two years ago, in his ninety-fourth year. Graduated from Harvard Medical School in 1867, he soon became a protégé of Morrill Wyman, with whom for many years he was intimately associated, and thus quickly acquired a place of prominence in his community. His name first appears as attending Council meetings about 1880. With Dr. John T. G. Nichols, he was appointed in 1886 one of the two first visiting physicians at the newly opened Cambridge Hospital. Primarily interested in surgery, he pioneered in this branch, along with Drs. Alfred Worcester, Edward R. Cutler and Henry O. Marcy. In association with Drs. Fred C. Shattuck and Samuel B. Woodward, as nominating councilor, he had a hand over a long period in the selection of properly qualified men for presidency of the state society.

In February, 1914, it was suggested that the state society abandon the separate publication of its proceedings and communications, and that, so far as possible, it publish these and all other official matters only in the *Boston Medical and Surgical Journal*. Dr. Stevens was a member of the special committee that studied and advised acceptance of the plan. When the affiliations became effective on July 1, 1914, the Society publications, begun in 1790, ceased as independent issues.

Malpractice defense and indemnity insurance are closely allied. The basis of the former in this state is an act adopted by the Massachusetts Medical Society in 1908, which follows the practice of many other state societies. It provides, under definite rules, for the defense, by the Society, of fellows against suits for malpractice, without expense to themselves. It does not, however, provide for the payment of any judgment rendered against a fellow. Because of an almost prohibitive rise in malpractice insurance rates in 1921, a movement was started to have the society provide indemnity insurance, but since its charter contained no such provision, other plans had to be considered. In October, a committee, of which Dr. Stevens was a member, was appointed to study the whole problem. Their conclusions, submitted two months later and embracing the plan now in

operation, were adopted. The plan seems to have worked satisfactorily.

A recent description by Dorothy Thompson of Winston Churchill applies so well to Dr. Stevens that I take the liberty of quoting it here: "There was something perennially young about him, as there is always something youthful about those who have done what they wanted to do, and have been happy. He had had a good life—the best life any man can have: a life of action and a life of intellect."

It is of interest to note that, in its one hundred and fifty-eight years of existence, the Massachusetts Medical Society has chosen as president no less than nine men from the Middlesex South District, whose combined terms equal eighteen years, and that sixteen of its one hundred and thirty-one orations have been delivered by men from this district. These men are as follows:

#### PRESIDENTS FROM MIDDLESEX SOUTH

William Kneeland	Cambridge	1784-1786
John Brooks	Medford	1823-1825
Josiah Bartlett	Concord	1862-1864
Alfred Hosmer	Watertown	1882-1884
Henry P. Walcott	Cambridge	1896-1898
George W. Gay	Chestnut Hill	1906-1908
Alfred Worcester	Waltham	1919-1921
Enos H. Bigelow	Frammingham	1923-1925
Charles E. Mongan	Somerville	1935-1937

#### ORATORS FROM MIDDLESEX SOUTH

John Brooks	Medford	1808
Josiah Bartlett	Charlestown	1810
Rufus Wyman	Charlestown	1830
William J. Walker	Charlestown	1845
Luther V. Bell	Somerville	1848
Horatio Adams	Waltham	1858
Morrill Wyman	Cambridge	1863
William W. Wellington	Cambridgeport	1870
Henry P. Walcott	Cambridge	1889
John T. G. Nichols	Cambridge	1893
Alfred Worcester	Waltham	1895
Zabdiel B. Adams	Frammingham	1897
John L. Hildreth	Cambridge	1906
Walter E. Fernald	Waverley	1912
Charles F. Painter	Newton	1925
Walter B. Cannon	Cambridge	1927

A detailed description of many of the other contributions made by members of Middlesex South District Medical Society to the progress of medicine in Massachusetts is impossible. Among them, to mention only a few, were the activities of G. J. Townsend, of Natick, in promoting the public-health and medical-practice acts; those of S. W. Abbott, of Newton, known for his contributions to the study of smallpox; those of George Curtis, whose administration as health officer in Newton for many years served, and will continue to serve, as a model for other cities; those of Godfrey Ryder, of Malden, chairman of a committee that in 1913 revised the Malpractice Act; those of Edward Cowles, of Waverley, under whose guidance McLean Hospital became the foremost semi-private institution of its kind in the country; and, finally, the long and efficient service rendered by Thomas M. Durrell, of Somerville, and George L. West, of Newton, as medical examiners, each of whom gave twenty eight years to this work.

Thus, the Middlesex South District Medical Society, starting out on its ninety-second year, may look back on its accomplishments with a certain amount of satisfaction and with the realization that as one of the units of the state society it has contributed its share toward the betterment of medicine in Massachusetts. And the future is bright with the assurance that the present members, inspired by the deeds of their predecessors, will meet the challenge and strive for still greater service.

270 Commonwealth Avenue

#### BIBLIOGRAPHY

- Burrage, W. L. *A History of the Massachusetts Medical Society, with brief biographies of the founders and chief officers, 1781-1922* 505 pp Boston (privately printed), 1923
- Cambridge Hospital Various annual reports
- Cutting, Miss M. S., Wayland, Massachusetts Personal communication
- Lear, T. The medical examiner system *J A M A* 89 579 583, 1927
- Morison, S. E. *Three Centuries of Harvard, 1636-1936*. 512 pp Cambridge Harvard University Press, 1936
- O'Hara, D. The heritage of Middlesex South *Boston M & S J* 197 60-68, 1927
- Thompson, D. There was a man a tribute to the rosy old warrior who made a nation know its peril *Life* 10 68 70, 1941
- Tyndale, T. H. The law of coroners. *Boston M & S J* 96 243 258, 1877.
- Viets, H. R. *A Brief History of Medicine in Massachusetts* 194 pp Boston Houghton Mifflin Co., 1930

## THE HYPERACTIVE CARDIOINHIBITORY CAROTID-SINUS REFLEX AS AN AID IN THE DIAGNOSIS OF CORONARY DISEASE

### Its Value Compared With That of the Electrocardiogram

LOUIS H. SIGLER, M.D.\*

BROOKLYN, NEW YORK

**I**N a recent communication, I<sup>1</sup> pointed out that slowing or stoppage of the heart induced by pressure on the carotid-sinus region may be used as an aid in the diagnosis of coronary disease. This assumption was based on a study of 1886 patients on whom the test was performed. The findings in this series corroborated my previous observations<sup>2-4</sup> that the cardioinhibitory reflex occurs much more frequently and in higher degrees of response in males than in females and in advancing age, conditions in which coronary disease is most prevalent. In the presence of demonstrable coronary disease, the reflex occurred oftenest and in the highest degrees.

The practical value of the test in the diagnosis of coronary disease was demonstrated in a number of cases. In many, a positive test was the only evidence of the presence of such disease at the time the test was performed. The following case is an example.

**CASE 1.** A 35-year-old man began to experience recurring left precordial pain, mainly after exertion. Physical examination 4 weeks after its onset showed nothing abnormal. The size and shape of the heart were normal, the rate was about 80 per minute, and the rhythm was regular. The sounds were of good quality, and no murmurs were heard. An electrocardiogram (Fig. 1A) likewise showed nothing abnormal. Pressure on the right carotid-sinus region, however, resulted in stoppage of the heart for several seconds. Pressure on the left yielded considerable slowing. This, together with the subjective symptoms, suggested the presence of coronary disease, even though no other evidence was present. Six weeks later, the patient developed a sudden spontaneous attack of retrosternal pain radiating to the left arm, which lasted all night. The pain was not relieved by nitroglycerin but required morphine for its relief. An electrocardiogram obtained 2 weeks after the attack (Fig. 1B) showed definite changes in the 4th precordial lead characteristic of infarction. The sedimentation rate of the blood cells was 18 mm. at 30 minutes and 24 mm. at 1 hour, which corroborated the diagnosis.

In occasional cases, a markedly hyperactive cardioinhibitory carotid-sinus reflex was present during an acute stage of myocardial infarction, and on recovery, cardioinhibition was greatly diminished. The following case is illustrative.

**CASE 2.** A 63-year-old woman, who had always been well, except for a low-grade hypertension, developed

shortness of breath and precordial oppression on exertion. This became much more marked after an episode of severe spontaneous precordial oppression lasting about 30 minutes. It was accompanied by a drop in systolic blood pressure from 190 to 115. Examination 1 week later showed slight left ventricular enlargement and moderate dilatation of the aorta. The heart rate was 90, and the rhythm was regular. The first and second heart sounds were greatly diminished in intensity, and there was a rough, short systolic murmur between the 3rd left costo-

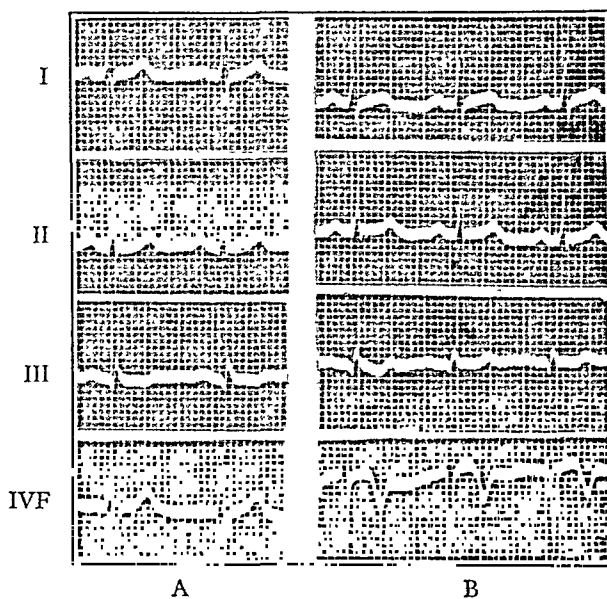


FIGURE 1.

A—normal electrocardiogram. B—electrocardiogram from the same patient eight weeks later and two weeks after an attack of coronary occlusion. The T waves in Lead 1 and the QRS complexes in Lead 3 are of lower voltage. The R waves in Lead 4 are small, and the T waves are markedly negative, whereas previously they were positive.

sternal junction and the apex. The lungs showed slight congestion at both bases. The electrocardiogram (Fig. 2A) showed low-voltage T waves in Lead 1, some depression of the RT segments and diphasic T waves in Leads 2 and 3 and abrupt QRST take-offs above the isoelectric line, with diphasic T waves, in Lead 4. The blood-cell sedimentation rate was 15 mm. at 30 minutes and 24 mm. at 1 hour. The blood pressure was 144/96. The findings definitely indicated recent myocardial infarction. Pressure on the right or left carotid sinus resulted in stoppage of the heart for several seconds.

The patient was seen again 2 months later, when the heart sounds were improved and the murmur had disappeared. The blood pressure was 162/98. The electro-

\*Attending cardiologist, Coney Island and Harper hospitals, Brooklyn, New York.

cardiogram (Fig 2B) showed positive T waves in Leads 1, 2 and 3, and markedly negative T waves in Lead 4. The RT segments in Leads 2 and 3 were slightly above the isoelectric line and rounded, and there were some changes in the QRS complexes in Lead 4. Carotid-sinus pressure at this time yielded marked slowing (+++) but no stoppage of the heart.

The patient was seen again 2 months later, when her condition had further improved. There was no precordial

occurred spontaneously and was not accentuated by exertion. At times, he also experienced some dizziness, cough and slight dyspnea. He applied for insurance disability, but his claim was rejected because the company cardiologist found his heart to be "perfectly normal."

Physical examination revealed the heart to be of normal size and shape with a rate of about 84 per minute and a regular rhythm. The heart sounds were within normal limits of intensity, quality and duration. A faint systolic

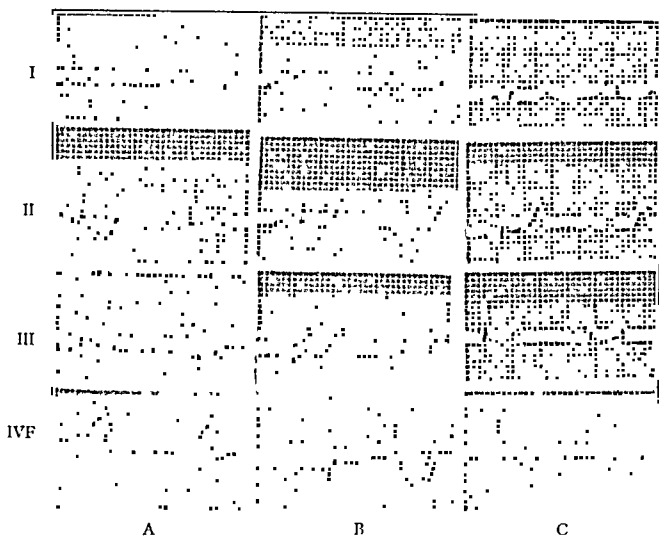


FIGURE 2

A—electrocardiogram one week after an episode of acute coronary occlusion. Biphasic T waves are noted in Leads 2, 3 and 4. B—electrocardiogram two months later. The T waves in Leads 2 and 3 are positive and in Lead 4 markedly negative. Changes are also noted in the QRS complexes in Lead 4, and in the QRS T segments in Leads 2, 3 and 4. C—electrocardiogram two months after B. Trivial T wave changes are noted in Leads 1, 3 and 4, indicating a practically static condition, with some improvement.

pain, and the heart sounds were moderately accentuated. The blood pressure was 170/94. The electrocardiogram (Fig. 2C) showed a slightly increased voltage of the T waves in Lead 1 and diminished negativity of the T waves in Lead 4. Carotid sinus pressure at this time resulted only in moderate slowing (+++).

In many cases, not only were the physical and electrocardiographic findings normal but even the subjective symptoms were not typical, and a hyperactive cardioinhibitory reflex was the only finding suggesting the diagnosis of coronary disease. The following case is an example.

CASE 3. A 60-year-old man, who was mildly diabetic, complained of occasional fleeting precordial pain, which

murmur at the apex was not transmitted. The aorta was moderately widened and tortuous, but the palpable arteries showed only a minimal amount of sclerosis. The blood pressure was 155-162/80-90. An electrocardiogram (Fig. 3) revealed nothing grossly abnormal, except for small Q waves in Lead 3, which in themselves were not significant, because the heart was transversely placed by a high diaphragm. Pressure on the right or left carotid sinus regions resulted in stoppage of the heart for several seconds. This finding, together with the presence of some aortic changes and the diabetic state, definitely suggested the presence of coronary disease.

Seven weeks after examination, the patient suddenly developed a typical attack of acute coronary occlusion and died within 1 hour.



RELATIVE FREQUENCY OF HYPERACTIVE CARDIO-INHIBITORY REFLEX AND ELECTROCARDIOGRAPHIC ABNORMALITIES IN CORONARY DISEASE

To determine the relative frequency of occurrence of the cardioinhibitory carotid-sinus reflex and of abnormalities in the electrocardiogram in coronary disease, I analyzed a series of 1073 cases showing definite evidence of such disease. Eight

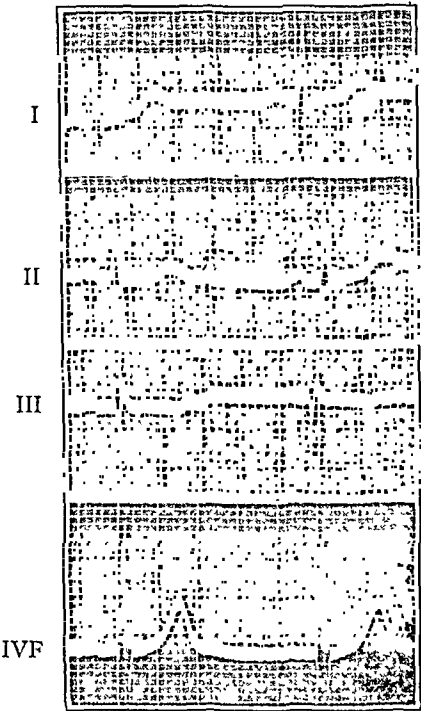


FIGURE 3.

*This electrocardiogram shows normal tracings except for the presence of Q waves in Lead 3, due undoubtedly to transverse position of the heart caused by a high diaphragm, since its voltage varied with changes in respiration.*

hundred and sixty-eight of these belonged to the group previously reported,<sup>1</sup> and 205 are new cases, observed since the last series was compiled. There were 784 males and 289 females in the entire group, and all grades of the disease were represented. The criteria used in the diagnosis were the same as those described previously.<sup>1</sup>

The degrees of cardioinhibition were divided into four groups as follows: +, when the slowing was less than 10 per cent; ++, when there was 10 to 30 per cent slowing; +++, when the slowing was 30 to 70 per cent; and +++, when the heart stopped for at least three seconds. The electrocardiograms were divided into five groups, as follows: normal; left-axis deviation but otherwise normal; slight changes; moderate changes; and marked changes.

In the cases showing slight electrocardiographic abnormalities were included those with slight deviations in the QRST segment and some changes in the QRS complex, with or without left-axis deviation. The changes in the QRS complex consisted of slight slurring or notching, low voltage, excessively high voltage and the presence of a Q wave in Lead 3. In the group showing moderate abnormalities were placed cases with the following changes: considerable slurring or notching of the QRS complex, with or without prolonged intraventricular conduction time up to 0.12 second; abnormally low voltage of the QRS segment; moderate changes in the QRST segment, such as elevation or depression of more than 1.5 mm. with rounding; and a negative T wave in Lead 1 alone, a negative or diphasic T wave in Leads 2 and 3, or a negative T wave in Lead 4 alone. Many cases had more than one of these abnormalities and showed, in addition, left-axis deviation.

In the group showing marked abnormalities were placed cases with the following changes: bundle-branch block; extremely low voltage of the QRS segment, with marked notching; considerable depression or elevation of the QRST segment; and a negative T wave in all leads or at least in Leads 1, 2 and 4 or Leads 1, 2 and 3. Most of these cases also showed left-axis deviation or, occasionally, right-axis deviation.

Table 1 summarizes the incidence of the cardioinhibitory response and of the abnormalities in the electrocardiograms in the entire series of 1073 cases. It will be seen that, in the male group,

TABLE 1. The Incidences of Cardioinhibitory Response and of Abnormal Electrocardiograms in 1073 Cases of Coronary Disease.

SEX	NO. OF CASES	NO. OF CASES SHOWING CARDIO-INHIBITION	NO. OF CASES WITH ABNORMAL ELECTROCARDIOGRAMS	
			INCLUDING LEFT-AXIS DEVIATION	EXCLUDING LEFT-AXIS DEVIATION
Male	784	716 (91.3%)	619 (78.9%)	494 (63.0%)
Female	289	210 (72.6%)	257 (88.9%)	208 (71.9%)

91.3 per cent showed the cardioinhibitory reflex, whereas only 63 per cent showed abnormalities in the electrocardiogram, if cases having only left-axis deviation are excluded, or 78.9 per cent if such cases are included. Among females, about the same percentage of cases showed cardioinhibition as abnormal electrocardiograms.

A comparative analysis was also made of the various degrees of cardioinhibition and of the electrocardiographic changes. This is shown in Table 2 and Figures 4 and 5. It will be seen that

only 37.4 per cent of the male group showed significant (moderate and marked) electrocardiographic changes, whereas 61.8 per cent showed marked (+++ and ++++) cardioinhibitory reactions. In the female group, 40.0 per cent showed

nomenon, unassociated with other reflexes of the carotid-sinus group, such as a marked fall in blood pressure and cerebral manifestations, including dizziness, sensory disturbances and syncope, previously described by Weiss and his co-workers<sup>6</sup> and

TABLE 2. *The Relation of Cardioinhibitory Response to the Degree of Electrocardiographic Change in 1073 Cases of Coronary Disease.*

		DEGREE OF CARDIOINHIBITION											
TYPES OF ELECTROCARDIOGRAMS	SEX	0		+		++		+++		++++		TOTALS AND PERCENTAGES	
		No of Cases	Per cent age	No of Cases	Per cent age	No of Cases	Per cent age	No of Cases	Per cent age	No of Cases	Per cent age		
Normal	Male	12	7.3	24	15.6	37	24.1	32	21.1	60	39.2	165	21.0
	Female	9	28.2	7	30.4	8	34.7	5	21.7	3	13.2	32	11.6
Left axis deviation	Male	11	8.8	16	14.0	35	30.7	2*	23.6	36	31.7	125	15.9
	Female	14	28.6	10	28.5	12	34.2	8	22.8	5	14.5	49	16.9
Slight changes	Male	20	10.0	25	13.8	41	22.5	51	28.0	65	35.7	202	25.7
	Female	31	33.4	20	32.2	20	32.2	12	19.3	10	16.3	93	32.1
Moderate changes	Male	15	7.7	27	14.8	41	22.5	45	24.7	69	38.0	192	25.5
	Female	17	26.6	9	19.3	13	27.6	13	27.6	12	25.5	64	22.1
Marked changes	Male	10	10.6	5	6.1	23	27.0	18	21.1	49	45.8	95	12.3
	Female	8	15.7	11	25.5	10	23.2	14	32.5	8	18.8	51	17.9
Totals and percentages	Male	68	8.7	97	13.5	177	24.7	173	24.1	269	37.7	784	100.0
	Female	79	27.4	57	27.1	63	30.0	52	24.7	38	18.2	284	100.0

gross electrocardiographic abnormalities, and 42.9 per cent marked cardioinhibition.

The table and charts also show that no relation exists between the degrees of cardioinhibition and electrocardiographic changes. The group with normal electrocardiograms showed approximately the same percentage of cases with the higher degrees of cardioinhibition as the groups with marked electrocardiographic changes.

### DISCUSSION

It appears from the findings presented here that a hyperactive cardioinhibitory carotid-sinus reflex occurs more frequently than abnormalities in the electrocardiogram in cases of coronary disease. This applies also to the higher degrees of hyperactivity, which are definitely abnormal manifestations and occur very infrequently in the absence of coronary disease. The test may therefore perhaps be considered to be of more diagnostic value than the electrocardiogram in the recognition of such disease.

Like any other test or method of examination, however, the hyperactive cardioinhibitory carotid-sinus reflex has its shortcomings and pitfalls. The facts that it does occur in cases other than coronary disease and that many cases of such disease show a negative response limit its usefulness in such diagnosis. This, however, applies also to the electrocardiogram and to all other means of diagnosis.

The test may perhaps be considered to be a definite sign in coronary disease under the following conditions: if it occurs as an independent phe-

by Smith<sup>4</sup>; if it occurs as the principal manifestation of the group of reflexes, the other signs, appearing either late or early, being dependent on this reflex for their production; and if it appears after comparatively slight pressure on the carotid-sinus region and no other vagal disturbances occur. Under such circumstances, one must assume that the selective augmentation of the induced vagal impulse is in the cardiac ganglions rather than in the ganglions of vagal centers in the medulla. If such augmentation occurred in the medullary centers, it would conceivably affect the entire vagal system rather than predominantly that of the heart.

In the present state of knowledge, only a theoretical explanation may be offered for the frequent occurrence of a hyperactive cardioinhibitory carotid-sinus reflex in coronary disease. As stated in the previous communication,<sup>1</sup> it is possible that local ischemia diminishes the resistance of the ganglions and of the myoneural junctions of the vagus nerves in the heart. Another explanation may be that the ischemic condition caused by coronary disease may produce local chemical changes that sensitize the vagal system in the heart. That there is some chemical relation between coronary disease and vagal activity is shown by the work of Loewi.<sup>7</sup> He brought forward experimental evidence to show that the vagus nerves produce a substance, which he<sup>8</sup> later considered to be identical with acetylcholine, that caused the same effect on the heart as vagal stimulation itself. The effect of the substance is neutralized by atropine. Hall, Ettinger and Banting<sup>9</sup> produced experimental coronary disease and myocardial damage in

animals by repeated injections of a 1:10,000 solution of acetylcholine daily over a period of months.

Whatever the explanation may be, I believe that the reflex has great practical value in the diagnosis

cause of the more advanced damage to the heart. The incidence of the hyperactive cardioinhibitory reflex, however, is likewise greater in such cases.

SUMMARY

A comparative study is presented of the incidence of a hyperactive cardioinhibitory carotid-sinus reflex and of electrocardiographic abnormalities in a series of 1073 cases, mostly ambulatory, of coronary disease. It was found that 91.3 per cent of the males and 72.6 per cent of the females in this series showed the cardioinhibitory response, whereas only 63 per cent of the males and 71.9 per cent of the females showed abnormalities in the electrocardiogram. High degrees of cardioinhibitory response, which are definitely abnormal, occurred in 61.8 per cent of the males and 42.9 per cent of the females. Marked electrocardiographic abnor-

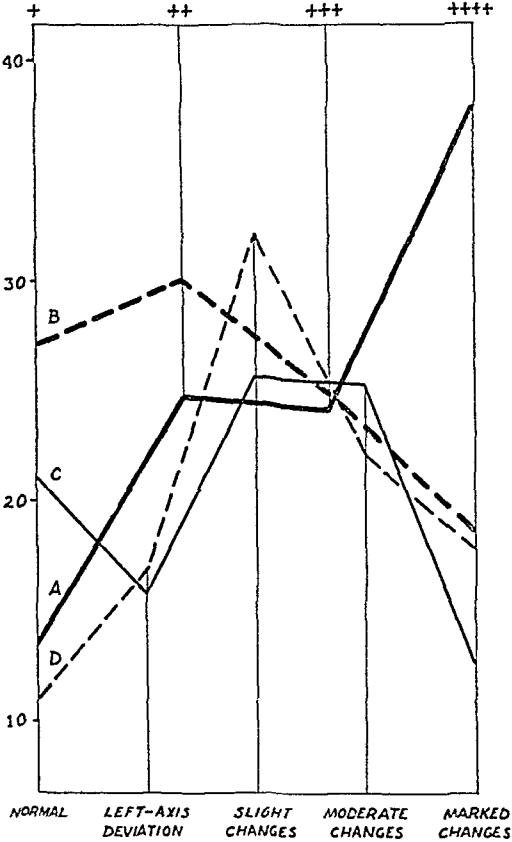


FIGURE 4. The Incidence of Cardioinhibitory Response and of Abnormal Electrocardiograms in a Series of 1073 Cases of Coronary Disease.

The ordinates represent the percentage of cases responding; the abscissas represent degrees of cardioinhibition and types of electrocardiographic changes.

Degrees of cardioinhibitory response are expressed in plus marks: + when the slowing was less than 10 per cent; ++ when there was 10 to 30 per cent slowing; +++ when the slowing was 30 to 70 per cent; and ++++ when the heart stopped for at least 3 seconds.

The designations for the types of electrocardiograms are described in the text.

A represents the male cardioinhibitory responses, and B the female; C represents the male electrocardiographic findings, and D the female.

of such disease among patients in the coronary age group who present suspicious subjective symptoms.

The cases covered by this investigation are predominantly ambulatory. In hospital material, the incidence and degree of electrocardiographic changes in coronary disease are much greater, be-

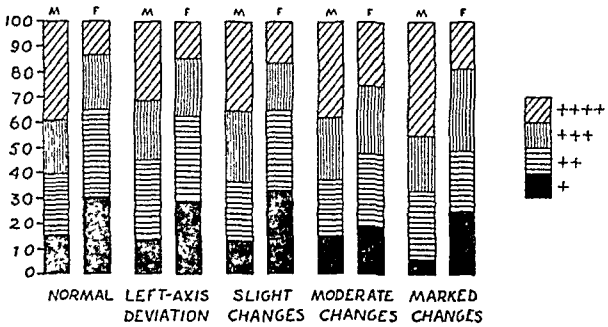


FIGURE 5. Degrees of Cardioinhibition, Expressed in Percentage of Cases, in Each Type of Electrocardiogram.

The descriptions of the degrees of cardioinhibition and the types of electrocardiograms are the same as those in Figure 4. M represents males; F, females.

malities occurred in only 37.4 per cent of the males and in 40 per cent of the females.

It is believed that the hyperactive cardioinhibitory carotid-sinus reflex may be used as an aid in the diagnosis of coronary disease in persons of the coronary age who present suspicious complaints. As such, it is often of greater value than the electrocardiogram, and will suggest the correctness of the diagnosis when the electrocardiogram may be entirely misleading.

The explanation for the frequency of the hyperactive reflex in coronary disease is at the present state of knowledge purely theoretical. It may be due to local ischemia in the heart, which lowers the resistance in the vagal ganglions and in the myoneural junctions, or which produces some chemical changes that sensitize the vagus nerves locally.

## REFERENCES

- 1 Sigler L. H. The hyperactive cardioinhibitory carotid sinus reflex: a possible aid in the diagnosis of coronary disease. *Arch Int Med* 67:1, 193 1941
- 2 *Idem* Clinical observations on the carotid sinus reflex. I. The frequency and the degree of response to carotid sinus pressure under various diseased states. *Am J M Sc* 186 110-118 1933
- 3 *Idem* Clinical observations on the carotid sinus reflex. II. The response to carotid sinus pressure at various ages and heart rates and rhythms. *Am J M Sc* 186 118 128 1933
- 4 *Idem* Further observations on the carotid sinus reflex. *Ann Int Med* 9 1380 1392 1936
- 5 Weiss S, Cappe R. B., Ferris E. B. and Munro D. Syncope and convulsions due to a hyperactive carotid sinus reflex. *Arch Int Med* 58 407-417, 1936
- 6 Smith H. L. Fainting attacks resulting from hypersensitive carotid sinus reflexes. *Am Heart J* 14 614 617 1937
- 7 Loewi O. Über Humorale Übertragbarkeit der Herznervenwirkung. *Arch f d ges Physiol* 189 739 242 1921
- 8 *Idem* The humoral transmission of nervous impulses. In *The Harvey Lectures* Series 28 233 pp. Baltimore: Williams & Wilkins Co 1934 1 p 218 233
- 9 Hall G. L., Ettlinger G. H., and Banting F. G. An experimental production of coronary thrombosis and myocardial failure. *Canad M J* 34 12 1936

## THE TREATMENT OF ANGINA PECTORIS WITH TESTOSTERONE PROPIONATE\*

### Preliminary Report

MAURICE A. LESSER, M.D.†

BOSTON

DURING the last few years, a number of observations have been reported on the genital as well as the extragenital effects of testosterone propionate. There are, however, only a few papers dealing with its action on the circulatory system. Ratschow and Klostermann,<sup>1</sup> in experimental work on rats, observed that an androgenic preparation prevented the sloughing produced by the vasoconstricting effect of ergotamine. Clinically, Arndt<sup>2</sup> reported favorable results in 8 male patients treated with testosterone propionate; 5 of these had peripheral vascular disease, and 3 had angina pectoris. Edwards, Hamilton, Duntley and Hubert<sup>3</sup> have described an increase in the cutaneous vascular bed in castrate and eunuchoid patients treated with testosterone propionate.

The effect of testosterone propionate on blood pressure in patients with hypertension is debatable, the number of cases studied being too small to be conclusive. Steinach, Peczenik and Kun<sup>4</sup> observed a significant fall in systolic pressure in 31 of 49 patients with hypertension, following treatment with either androsterone benzoate or testosterone propionate. On the other hand, Greene<sup>5</sup> found no significant change in the blood pressure levels in 21 patients who had been treated with testosterone propionate for senile enlargement of the prostate; the majority of whom had hypertension.

Edwards, Hamilton and Duntley<sup>6</sup> observed beneficial effects from testosterone propionate in peripheral vascular disease. Three patients with thromboangitis obliterans (Buerger's disease) and 4 with peripheral arteriosclerosis showed early, definite skin vascularization.

In view of these observations, 24 patients with angina pectoris were given testosterone propionate in an attempt to ascertain whether this form of treatment would influence either the frequency or the severity of the attacks.

### METHODS AND RESULTS

Since June, 1939, 20 men and 4 women, varying in age from forty to seventy-seven years, have been treated with testosterone propionate for angina pectoris. In all these patients, the diagnosis of angina pectoris was clearly established, and was based on a history of typical attacks of substernal or precordial pain precipitated by exertion or emotion and quickly relieved by rest or by nitroglycerin. Each of the patients selected for this study experienced at least one anginal attack daily, and the majority had several. Most of the patients were treated during the fall and winter months, at a time when climatic conditions made them more subject to anginal attacks. These patients were given no medication except nitroglycerin to relieve an attack, were kept ambulatory and were encouraged to perform their usual duties.

Twenty five milligrams of testosterone propionate dissolved in 1 cc. of sesame oil<sup>7</sup> was given intramuscularly every second to fifth day, depending on the frequency and severity of cardiac pain and the response to treatment, for a total of between five and twenty five injections, with an average of eleven injections. No untoward reactions were noted. The dosage was chosen arbitrarily, and it is possible that smaller amounts of the drug may give equally good results.

All patients in this series improved under testosterone propionate treatment, but the improve-

\*From the Massachusetts Memorial Hospitals and the Department of Bacteriology, Public Health and Preventive Medicine, Boston University School of Medicine.

†Instructor in preventive medicine, Boston University School of Medicine; visiting physician, Massachusetts Memorial Hospitals.

<sup>7</sup>Kindly supplied by Ciba Pharmaceutical Products, Incorporated, Summit, New Jersey, under the trade name of Perandren.

TABLE 1. *Results of Testosterone Propionate Treatment in Cases of Angina Pectoris.*

CASE No	AGE	SEX	DURATION OF ANGINA	LIMIT OF PHYSICAL ACTIVITY BEFORE TREATMENT	BLOOD PRESSURE BEFORE TREATMENT	BLOOD PRESSURE AFTER TREATMENT	NO OF INJECTIONS BEFORE IMPROVEMENT	TOTAL NO OF INJECTIONS	LIMIT OF PHYSICAL ACTIVITY AFTER TREATMENT	DURATION OF IMPROVEMENT WITHOUT FURTHER TREATMENT	REMARKS
										mo	
1	52	F	3	Pain on climbing 1 flight of stairs or walking 2 blocks	150/90	110/75	3	14	No pain on climbing 1 flight of stairs or walking 9 blocks	5	Patient died of acute cardiac infarction 1 year after treatment was discontinued
2	68	M	6	Pain on climbing 1 flight of stairs	155/85	125/80	2	5	No pain on climbing 3 flights of stairs	7	Improvement maintained to date
3	40	M	3/4	Pain on climbing 1 flight of stairs or walking 6 blocks	120/80	110/80	2	5	No pain on climbing 3 flights of stairs or walking 1 mile	8	Improvement maintained to date
4	65	M	1	Pain on climbing 1 flight of stairs or walking 3 blocks	125/75	170/75	2	12	No pain on climbing 2 flights of stairs or walking 1 mile	6	Improvement maintained to date
5	54	M (2 weeks)		Pain on climbing 1 flight of stairs	120/90	85/65	3	8	No pain on climbing 3 flights of stairs	12	Patient has returned to work as a steamfitter
6	61	M	7/12	Pain on climbing 1 flight of stairs or walking 2 blocks	170/95	155/90	2	25	No pain on climbing 2 flights of stairs or walking 1/2 mile	3	Because of minor, intermittent anginal attacks treatment continued for 6 months
7	66	M	2	Pain on climbing 1 flight of stairs or walking 2 blocks	140/80	100/60	2	14	No pain on climbing 3 flights of stairs or walking 1 mile	6	Patient died suddenly 6 months after treatment was discontinued
8	64	M	1/2	Pain on climbing 1 flight of stairs or walking 50 yards for 1 year unable to work as electrician	170/90	145/90	4	10	No pain on climbing 3 flights of stairs or walking 2 miles, back to work as electrician	7	After recurrence of anginal attacks, second course of 10 injections with freedom of attacks for 2 months third course of 5 injections given, with improvement of 2 months' duration, improvement maintained to date
9	62	M	3	Pain on climbing 3 to 4 stairs or walking 3 blocks	140/90	110/80	5	9	No pain on climbing 54 stairs or walking 1 mile	4 1/2	Patient died of acute cardiac infarction 4 1/2 months after treatment was discontinued, but was entirely free of anginal attacks in the interim
10	50	M	3 1/2	Pain on climbing 7 stairs or walking 2 blocks	120/80	105/70	2	5	No pain on climbing 2 flights of stairs or walking 1/2 mile	5	Patient reported that his feet had become warm for the first time in 3 years
11	66	M	3	Pain on climbing 1 flight of stairs or walking 100 yards	165/80	135/80	4	20	No pain on climbing 3 flights of stairs or walking 1 mile	2	Treatment continued for 4 months because of occasional mild anginal pain second course of 6 injections given because of recurrence of symptoms, with excellent results
12	57	M	1/4	Pain on climbing 1 flight of stairs or walking 3 blocks	150/80	118/85	1	6	No pain on climbing 2 flights of stairs or walking 12 blocks	10	
13	56	M	3	Pain on walking 2 blocks	170/40	120/40	3	13	No pain on walking 1 mile	3	Patient has syphilitic aortitis with aortic regurgitation
14	52	M	1 1/2	Pain on walking 3 blocks	140/80	100/75	3	13	No pain on walking 2 miles	3	
15	49	M	1 1/2	Pain on climbing 1 flight of stairs or walking 4 blocks	240/130	180/100	2	7	No pain on climbing 2 flights of stairs or walking 1 mile	10	
16	66	M	1/6	Pain on climbing 1 flight of stairs or walking 1 block	150/90	120/80	3	6	No pain on climbing 1 flight of stairs or walking 10 blocks	8	
17	70	M	1/12	Pain on climbing 1 flight of stairs or walking 2 blocks	165/90	140/80	2	8	No pain on climbing 3 flights of stairs or walking 10 blocks	2	
18	55	M	1	Pain on walking 1 block, for 1 year, unable to work	140/75	130/80	3	13	No pain on walking 1 mile, has returned to work as machinist		Treatment just completed

TABLE 1 (Concluded).

CASE No	Age	Sex	DURATION OF ANGINA	LIMIT OF PHYSICAL ACTIVITY BEFORE TREATMENT	BLOOD PRESSURE BEFORE TREATMENT	BLOOD PRESSURE AFTER TREATMENT	NO OF INJECTIONS BEFORE TREATMENT	TOTAL NO OF INJECTIONS	LIMIT OF PHYSICAL ACTIVITY AFTER TREATMENT	DURATION OF IMPROVEMENT WITHOUT FURTHER TREATMENT	REMARKS
	yr		yr.							mo.	
19	54	M	1	Pain on climbing 1 flight of stairs or walking 3 blocks	120/80	100/60	4	14	No pain on climbing 3 flights of stairs or walking 1 mile		Treatment just completed
20	69	F	5	Pain on climbing 10 stairs or walking 2 blocks	190/105	120/80	6	12	No pain on climbing 19 stairs or walking 6 blocks		Patient died of acute cardiac infarction 2½ months after treatment was begun, while under treatment, anginal attacks were less frequent and considerably less severe.
21	50	F	4	Pain on climbing 1 flight of stairs	145/90	120/80	3	9	No pain on climbing 3 flights of stairs		Still under treatment
22	77	M	8	Pain on climbing 3 stairs or walking 1 block	140/90	130/80	1	8	No pain on climbing 1 flight of stairs or walking ½ mile	2	Improvement maintained to date
23	62	F	1	Pain on climbing 6 stairs or walking 1 block	180/100	140/70	4	10	No pain on climbing 15 stairs or walking ½ mile		Still under treatment
24	56	M	7	Pain on climbing 1 flight of stairs	160/80	130/80	3	9	No pain on climbing 2 flights of stairs		Still under treatment

ment was much greater in the men than in the women. The latter group is as yet too small to permit proper evaluation of the significance of sex on the efficacy of this therapy.

Two patients showed definite improvement after one injection, 8 after two, 8 after three, 4 after four, 1 after five, and 1 after six. Improvement was determined by the subjective report of the patient concerning a decrease in the frequency and severity of the attacks while continuing his usual routine, and by the ability of the patient to increase his physical activity without precipitating an attack. The beneficial effect of this course of treatment has been observed for as long as twelve months after the discontinuation of therapy.

Five patients were given six consecutive injections of sterile sesame oil prior to receiving testosterone propionate, and 2 were similarly controlled after a recurrence of their anginal symptoms following their first course of the drug. None of the patients who had received sterile sesame oil alone showed any appreciable change in symptoms. This was in marked contrast to the general improvement noted in the patients treated with testosterone propionate. The contrast was particularly striking in the 2 patients who were first treated with testosterone propionate with remarkable improvement (Cases 8 and 11, Table 1), and then had a recurrence of symptoms four and seven months, respectively, after the last injection. For these new attacks, they were given placebo injections of sterile sesame oil, without clinical improvement. Following a return to testosterone propionate therapy, relief of anginal attacks was again obtained.

Of interest is the fact that in the majority of the patients there was a lowering of blood pressure during the course of testosterone propionate therapy, but it is questionable whether any significance can be attached to this.

Fluoroscopic examinations, serial kymograms and electrocardiograms showed no uniform changes resulting from this therapy.

#### DISCUSSION

Angina pectoris has been shown to be the result of myocardial ischemia, developing from a greater demand for coronary blood flow than can be supplied at the given instant.<sup>7</sup> This discrepancy between supply and demand is most frequently associated with a narrowing of the coronary arterial bed. It has further been indicated that, in cases of angina pectoris unassociated with either hypertension or valvular disease, there are occlusions of the major coronary arteries.<sup>7,8</sup> Since the pathologic basis for angina pectoris is relative anoxia of the myocardium, therapy has been directed toward improving the coronary circulation. This can be accomplished either by vasodilatation of existing vessels or by promoting collateral circulation.

Vasodilating drugs, such as nitroglycerin and the xanthine derivatives, have enjoyed widespread use in the treatment of angina pectoris. These have been shown to increase coronary flow directly by vasodilatation of the coronary arteries.<sup>9</sup> This effect, however, is only transitory.

Improved myocardial blood supply is the major desideratum in the control of angina pectoris. This problem has been approached surgically with some success, but such methods have definite limitations

because of the operative risk.<sup>10-12</sup> The observations of Gross<sup>13, 14</sup> indicate that anastomotic channels between the right and left coronary arteries develop to an increasing degree with advancing age. From more recent studies on the coronary circulation, it has become apparent that the development of these anastomotic channels is dependent on partial or complete occlusion of one or more major coronary arteries.<sup>15, 16</sup> Furthermore, in post-mortem examinations, the adequacy of such collateral circulation in some cases has been proved by the lack of significant myocardial damage in the presence of obstructive arterial lesions of long duration.<sup>7</sup> Whether the improvement noted with testosterone propionate in the treatment of patients with angina pectoris, as well as the results obtained by Edwards, Hamilton and Duntley<sup>6</sup> in the peripheral circulation, can be ascribed to the development of collateral channels is a matter of speculation.

In contrast to that of nitroglycerin, the action of testosterone propionate is not instantaneous, and does not relieve an acute attack. Its action is only gradually discernible, the majority of the patients showing clinical improvement only after several injections. On the other hand, relief obtained was persistent, ranging from two to twelve months after treatment was discontinued.

Since the initiation of this investigation, Walker<sup>17</sup> has published data on patients with cardiovascular disease; 5 of these exhibited the syndrome of angina pectoris. Treatment with testosterone propionate led to definite improvement in 4 cases, whereas 1 patient was not benefited; however, the details of treatment in this latter case were not given. Increase in exercise tolerance, decrease in severity of pain and a general increase in strength were noted as manifestations of improvement. Recently, Bonnell, Pritchett and Rardin<sup>18</sup> also reported favorable results in 5 men with angina pectoris who were treated with an androgenic substance obtained from urine.

#### SUMMARY

Twenty-four patients, 20 men and 4 women, varying in age from forty to seventy-seven years, in whom the diagnosis of angina pectoris was clearly established, were treated with testosterone propionate.

Twenty-five milligrams of the drug was administered intramuscularly every second to fifth day for a total of between five and twenty-five injections, with an average of eleven injections.

Favorable results were obtained in all cases in that the frequency, severity and duration of attacks of angina pectoris were diminished, and these patients have been able to increase their physical ac-

tivities to a considerable degree without precipitating attacks. The beneficial effects of this treatment persisted between two and twelve months after treatment was discontinued.

The improvement in the men was much greater than in the women, although the latter group is too small to permit proper evaluation.

No appreciable improvement was noted following control injections of plain sesame oil, although the same patients responded when placed on testosterone propionate therapy.

No untoward effects were observed in any of the patients studied.

Fluoroscopic examinations, serial kymograms and electrocardiograms showed no uniform changes resulting from this therapy.

In view of the therapeutic response and the absence of untoward reactions, it is believed that testosterone propionate may prove to be a valuable drug in the treatment of angina pectoris and warrants further investigation.

452 Beacon Street

#### REFERENCES

1. Ratschow, M., and Klostermann, H. C. Experimentelle Befunde zu Gefäßwirkung der Sexualhormone und ihre Beziehungen zur Klinik der peripheren Durchblutungsstörungen. *Ztschr. f. klin. Med.* 135:191-211, 1938.
2. Arndt, H. Zur Therapie extragenitaler Störungen mit Sexualhormonen. *Wien. med. Wchnschr.* 89:222-227, 1939.
3. Edwards, E. A., Hamilton, J. B., Duntley, S. Q., and Hubert, C. Cutaneous vascular and pigmentary changes in castrate and eunuchoid men. *Endocrinology* 28:119-128, 1941.
4. Steinich, E., Peczenik, O., and Kun, H. Über hormonale Hypoämierung, insbesondere über den Einfluss der männlichen Sexualhormone und ihrer Kombination mit weiblichem Hormon auf erhöhte Blutdruck und Hypertonus. *Wien. klin. Wchnschr.* 51:65-67, 102-103, 134-139, 1938.
5. Greene, R. On the effect of testosterone propionate on blood pressure. *Lancet* 2:79, 1938.
6. Edwards, E. A., Hamilton, J. B., and Duntley, S. Q. Testosterone propionate as a therapeutic agent in patients with organic diseases of the peripheral vessels: preliminary report. *New Eng. J. Med.* 220:865-1939.
7. Blumgart, H. L., Schlesinger, M. J., and Zoll, P. M. Angina pectoris, coronary failure and acute myocardial infarction: role of coronary occlusions and collateral circulation. *J. A. M. A.* 116:91-97, 1941.
8. Davis, D., and Klainer, M. J. Studies in hypertensive heart disease. III. Factors in the production of angina pectoris. *Am. Heart J.* 19:198-205, 1940.
9. Wegria, R., Essex, H. E., Herrick, J. F., and Mann, F. C. The simultaneous action of certain drugs on the blood pressure and its flow in the right and left coronary arteries. *Am. Heart J.* 20:557-571, 1940.
10. Beck, C. S. Development of a new blood supply to the heart by operation. *Ann. Surg.* 102:801-813, 1935. Further data on the establishment of a new blood supply to the heart by operation. *J. Thoracic Surg.* 5:604-611, 1936.
11. O'Shaughnessy, L. The pathology and surgical treatment of cardiac ischaemia. *Bristol Med. Chir. J.* 54:109-126, 1937. Surgical treatment of cardiac ischaemia. *Lancet* 1:185-194, 1937.
12. Strieder, J. W., Clute, H. M., and Graybiel, A. Cardio-omentalpex in the treatment of angina pectoris: report of two cases. *New Eng. J. Med.* 222:41-47, 1940.
13. Gross, L. *The Blood Supply to the Heart in Its Anatomical and Clinical Aspects*. 171 pp. New York: Paul B. Hoeber, 1921.
14. Gross, L., and Kugel, M. A. The arterial blood vascular distribution to the left and right ventricles of the human heart. *Am. Heart J.* 9:165-177, 1933.
15. Schlesinger, M. J. An injection plus dissection study of coronary artery occlusions and anastomoses. *Am. Heart J.* 15:528-568, 1938.
16. Blumgart, H. L., Schlesinger, M. J., and Davis, D. Studies on the relation of the clinical manifestations of angina pectoris, coronary thrombosis and myocardial infarction to the pathologic findings, with particular reference to the significance of the collateral circulation. *Am. Heart J.* 19:1-91, 1940.
17. Walker, T. C. The use of testosterone propionate and estrogenic substance in cardiovascular disease: preliminary report. *Med. Rec. & Ann.* 34:667, 1940.
18. Bonnell, R. W., Pritchett, C. P., and Rardin, T. F. Treatment of angina pectoris and coronary artery disease with sex hormones. *Ohio State M. J.* 37:554, 1941.

## USE OF THE ASPIRATING NEEDLE IN THE DIAGNOSIS OF SOLITARY RENAL CYST\*

BANCROFT C. WHEELER, M.D.†

WORCESTER, MASSACHUSETTS

THE preoperative diagnosis of solitary cyst of the kidney can rarely be made with complete assurance. It is particularly difficult and very often impossible to distinguish between cyst and tumor, for the same symptoms and physical findings may be produced by each. Hematuria is commoner with tumor, although it also occurs with cyst, in some series as high as 25 per cent being reported. Roentgenography may be helpful but is rarely conclusive, since any or all of the criteria for the x-ray diagnosis of cyst are equally applicable to tumor. These are, as defined by Braasch<sup>1</sup> and by Greenberg et al.<sup>2</sup>: a rounded bulge in the renal outline; alteration of the normal position or axis of the kidney; compression deformities of the pelvis and calyces; deformity and compression of the ureter; pressure on adjacent organs; and calcification. Braasch has summarized the situation as follows: "In most cases uncomplicated renal cyst needs no treatment. However, the difficulty of clinical differentiation between simple cyst and neoplasm is the usual cause for surgical exploration, and in fact makes such exploration necessary in almost every case of renal cyst."

It is naturally of purely academic interest to attempt clinical distinction between the two conditions if one believes that all cysts should be operated on. A difference of opinion exists on this point, some urologists holding that, if a cyst produces no symptoms, there is no need for operation. Lately, the possibility of treating cysts by aspiration has once more been discussed. In 1939, Fish<sup>3</sup> presented 2 cases that, since operation was contraindicated, were successfully treated by aspiration and instillation of 50 per cent glucose as a sclerosing agent. The glucose was used when the cyst fluid reaccumulated after a single aspiration. More recently, a series of 15 cases was reported by Dean,<sup>4</sup> who used aspiration alone as the procedure of choice. There were no complications, and the fluid did not reaccumulate.

Aspiration as a routine form of treatment has been generally regarded as unsuitable because of the possible coexistence of tumor in the same kidney. The type of tumor to be chiefly feared ap-

pears to be not a separate and distinct growth, which would be no likelier to occur in conjunction with a cyst than in any kidney, but the rare form called "hypernephric cysts." These, according to Hepler,<sup>5</sup> are cysts with thick fibrous walls containing small islands of carcinoma. The cyst fluid may be clear. Hypernephric cysts are not common, but their occurrence<sup>6</sup> constitutes the strongest argument against the routine use of aspiration therapy.<sup>7</sup> It may be noted in passing that one common form of surgical treatment—namely, excision of the extrarenal portion of the cyst and carbolicization of the remainder—may well be ineffective in this type if unrecognized. Aspiration may be employed to advantage, however, in the treatment of cases in which symptoms are distressing but operation is contraindicated.

It is in the field of differential diagnosis, I believe, that aspiration can be most valuable. The procedure is simple and, if carefully done, carries practically no risk. In fact, Dean<sup>4</sup> has performed aspiration biopsies on 150 solid renal tumors, without mishap. Since nothing is injected, the chief hazards of perirenal air insufflation are avoided. Even if operation is contemplated, the definite establishment of the diagnosis of cyst in a case in which a large mass is present may permit the operator to select the lumbar approach rather than the abdominal. Again, if one is dealing with an asymptomatic mass connected with the kidney, the finding of clear fluid on aspiration raises a distinct question of the need of operation, especially when any deterring factors exist. Before aspiration, it is, of course, essential to have satisfactory x-ray studies, including at times a barium enema, to determine definitely the anatomic relation of the colon to the cyst.

In the following cases of solitary cyst, in which the suspected diagnosis was confirmed by aspiration, neither patient was operated on. One, having been observed for sixteen months, affords some additional information concerning the rate of reaccumulation of fluid. Data on this point in the literature are inconclusive because so few cases have been followed. If, with the reporting of a

\*Presented at a meeting of the New England Section of the American Urological Association, Boston, April 24, 1941.

†Assistant visiting surgeon, Memorial Hospital, Worcester, Massachusetts.

Since presenting this paper, I have observed a case of hypernephric cyst. A patient with a mass attached to the kidney diagnosed solitary cyst by x-ray study and with clear fluid obtained on aspiration was subsequently explored because of persistent pain. The kidney was found to contain adenocarcinoma in the cyst wall and in the immediately adjacent renal tissue and was removed.



significant number of observations, it appears that reaccumulation may take years, urologists will be more inclined than at present to employ aspiration as a therapeutic measure in selected cases.

### CASE REPORTS

CASE 1. J. H. G., a 56-year-old man, entered the Worcester Memorial Hospital on December 30, 1939, complaining of painless hematuria occurring intermittently during the preceding 2 days. He had no other urinary symptoms and considered himself to be in good general health. The previous history was noncontributory, except that the patient had had an appendectomy in 1933 and a herniorrhaphy 4 years later. The urinary sediments reported during these hospital entries were normal.

The patient was moderately obese and of a plethoric type. Physical examination showed no costovertebral tenderness; neither kidney could be felt. The urine was grossly bloody, but other laboratory findings were within normal limits. Through the cystoscope, the blood was seen to be coming from the right ureteral orifice, and on ureteral catheterization, the urine from this side was bloody whereas that from the left was clear. Cultures from both kidneys were negative. A flat x-ray film showed the lower pole of the right kidney to be opposite the 3rd lumbar interspace. In the region of the upper pole, there was a large, rounded soft-tissue mass, with a sharp outline and of homogeneous density. Retrograde pyelograms showed the upper calyces of the right kidney to be displaced downward. The left kidney pelvis appeared normal. From these findings, the roentgenologist made a diagnosis of probable solitary cyst.

Largely to confirm this diagnosis, aspiration was carried out a few days later. The patient was prepared as if for a right nephrectomy, and all plans were made to proceed with this in the event of a dry tap. Under light general anesthesia, a lumbar-puncture needle was inserted below the 12th rib on the right, just lateral to the spinal muscles in a direction inward, upward and slightly forward. A definite sensation of entering a cavity was not made out; when the desired depth was reached, however, the obturator was removed, and clear yellowish fluid obtained—325 cc. being aspirated. On examination, the fluid showed the following characteristics: alkaline reaction, specific gravity 1.012, sugar 117 mg., total protein 2.4 gm. and chlorides 610 mg. per 100 cc. and a few red blood cells per high-power field in the sediment.

On the following day, the patient felt perfectly well and has been so ever since, except for a mild intermittent lumbar backache, starting on the right, and present chiefly when he is tired. This pain had never been present previously, its first occurrence being about 2 weeks following the aspiration. What connection, if any, there may be is not clear. It has become no worse in the past year. The patient had a single recurrent episode of hematuria 8 months later.

The size of the cyst has been followed at intervals. An intravenous pyelogram taken 2 days after aspiration showed neither downward displacement of the kidney nor pressure defect of the upper calyces. Instead of the large shadow previously noted, a small nub of tissue could be seen projecting from the upper pole. A month later, there was an appreciable increase in the size of this mass, and 8 months later it appeared to be about a quarter to a third as large as originally, slight depression of the upper calyces reappearing. In a recent flat x-ray film, however, 16 months after aspiration, the mass did not seem to have increased appreciably.

*Comment.* It is possible that operation must at some future time once more be considered in this case. However, if clearly related symptoms should recur, aspiration could again be done with hope of relief. The so-called "hypernephric cyst" cannot, of course, be entirely ruled out.

CASE 2. Z. R., a 61-year-old woman, was referred to the Worcester Memorial Hospital on June 12, 1940, because of the incidental finding of an abdominal mass by her physician. She had sought relief from transient headaches and dizzy spells. The history otherwise was irrelevant. The patient had always been in good general health.

On physical examination, the only positive finding of note was a mass the size of an orange in the left upper abdomen. It was rounded, smooth, movable and non-tender. The urinary sediment contained many white blood cells and cocci per high-power field. At cystoscopy, the bladder appeared characteristic of mild chronic cystitis. Specimens of urine were obtained from both kidneys, cultures subsequently showing *Staphylococcus aureus* from each. In retrograde pyelograms, the right kidney pelvis looked normal. The mass appeared attached to the lower pole of the left kidney and moved with it. The lower calyces were pushed upward slightly. A subsequent barium enema showed that the descending colon was displaced forward by the mass. Again, the roentgenologist was reasonably sure of the diagnosis of cyst.

Since the patient had no symptoms referable to the left kidney, it was decided to ascertain, if possible without operation, whether the mass was a cyst. She was accordingly prepared as for left nephrectomy, and under general anesthesia a lumbar-puncture needle was introduced lateral to the spinal muscles in the direction indicated by the x-ray films. The mass was steadied, and counterpressure exerted with the left hand. The motion of the needle with respiration was helpful in indicating that the kidney had been reached. Fluid was encountered, and about 150 cc. aspirated. No more could be obtained on attempted adjustment of the needle in the same plane, although it was realized that more fluid was almost undoubtedly present. There were no aftereffects, and the patient was discharged a few days later. She has been seen at intervals since then, the last time a month ago, or 9 months after aspiration. The mass has been palpable at all times, and showed only slight diminution in size after withdrawal of fluid. The patient remains entirely asymptomatic.

*Comment.* Aspiration in this case was purely a diagnostic procedure. Inability to withdraw more fluid may have been due to collapse of the cyst wall against the tip of the needle, to dislodgment of the needle from the cavity, or to the fact that the cyst was multilocular. Again, the possibility that this was a "hypernephric cyst" cannot be ruled out.

### CONCLUSION

Aspiration is a simple procedure of value in the differential diagnosis of solitary cyst and tumor of the kidney.

27 Elm Street

### REFERENCES

1. Braasch, W. F.: discussion of Quinby, W. C., and Bright, E. F. Solitary renal cysts: their symptoms when situated at the upper pole of the right kidney. *J. Urol.* 33:201-214, 1935.
2. Greenberg, B. E., Brodny, M. L., and Robins, S. A. Solitary cysts of the kidney. *Am. J. Surg.* 23:271-283, 1934.
3. Fish, G. W. Large solitary serous cysts of the kidney. *J. A. M. A.* 112:514-518, 1939.

- 4 Dean A. L. Treatment of solitary cyst of the kidney by aspiration. *Tr. Am. A. Gen. & Urol. S. Soc.* 32:91-95, 1933.  
 5 Hepler A. B. A discussion of Dean's.  
 6 Ezckson W. J. and Green L. B. Solitary cyst of the kidney with adenocarcinoma in the walls of the cyst. *J. Urol.* 38:153-159, 1937.

## DISCUSSION

PRESIDENT ROGER C. GRAVES: This is a very interesting paper on a subject concerning which there may well be some discussion. One must weigh all the evidence, as Dr. Wheeler has said, and consider the advisability of aspirating a lesion that may be malignant, one must also consider the possibility of the risk that may be involved in dissemination of tumorous cells along the path of the needle outside the cyst or tumor, and one must decide wherein lies the greater risk in assuming the presence of a cyst and not operating, or in assuming the possibility of a tumor and preferring surgical exploration.

DR. G. G. SMITH (Boston): I remember only too vividly a woman who had what I was sure was a cyst. I asked her to come back in six months, and she did not show up for three years, by which time she had a clearly developed large tumor of the lower pole of the kidney, she died following operation. This was some years ago but if I had heard about Dr. Wheeler's paper at that time, I might have succeeded in getting a good effect. I believe it is not always easy to differentiate tumor and cyst. A short while ago, I operated on a man who had what looked like a typical cyst, a very large, round tumor below the kidney. Braasch states that a cyst throws a denser shadow than a tumor, and this man had quite a

heavy shadow, I thought it was a cyst, but the radiologist pointed out that several spots on the outline of the mediastinum were very significant of tumor, at least of a metastasis. I operated on the patient, as I should have anyway, because it was a large tumor, and it did turn out to be a very malignant tumor. I think, however, that Dr. Wheeler's experiences should be borne in mind.

A PHYSICIAN: I should like to ask if Dr. Wheeler has used fluoroscopy in these cases and if that would aid in differentiation.

DR. C. L. DEMING (New Haven): I have often wondered why, instead of aspirating, one does not inject iodide or some such fluid which would produce a definite cystogram and might be of distinct advantage in making a differential diagnosis. Has Dr. Wheeler thought of that possibility?

DR. WHEELER (closing): I have not used fluoroscopy. I think it might help in differentiating tumor and cyst, but it would still leave a good deal of doubt in certain cases. The main point to be borne in mind, it seems to me, is the possibility of tumor, particularly the hypernephric cyst. I have never seen any in my limited experience. I should be interested to know how common they are. So far as the injection of cysts is concerned, that has been done, although I have never tried it. Fish injected air and watched the rate of reaccumulation of fluid in his 2 cysts.

## MEDICAL PROGRESS

## ABDOMINAL SURGERY

ARTHUR W. ALLEN, MD\*

BOSTON

## ANESTHESIA

**S**O CALLED "continuous" novocain spinal anesthesia, as advocated by Lemmon,<sup>1</sup> is gaining favor. The technical difficulties are not great when careful attention to details is observed. The advantages are the greater safety of the anesthetic drug used, and the short duration of the action of novocain, which makes it possible to carry out operations of any length of time. If this method is supplemented by splanchnic block from within the abdomen, it comes near the ideal sought for safe anesthesia in operations on the stomach and duodenum. It is my opinion that this method will become well standardized and will supplant the more toxic but longer lasting agents now in use for extensive procedures.

Bronchoscopy, adequately to remove secretions from the bronchial tubes in some patients after

operation, is so vital that all anesthetists should be trained in this technique. Routine removal of bronchial secretions as advocated by Haight and Ransom,<sup>2</sup> can be carried out to great advantage on the wards by the resident staff.

## SUTURE MATERIAL

It is asserted that cotton thread is a better material for ligatures and sutures than silk or catgut,<sup>3,4</sup> and the use of cotton in a wide variety of conditions during the last six months at the Massachusetts General Hospital has substantiated these claims. Cotton is easier to handle than silk, since it is slightly rougher and the knot is more easily set, also, the unused portions do not stick to the glove as those of silk do. It is easily sterilized by boiling or autoclaving. If cotton is wound on rubber tubing, the shrinkage that occurs when it is boiled compresses the tubing slightly and does not weaken the fibers. In corresponding sizes it is stronger than unwaxed silk. It is well tolerated in the tissues and is not extruded even in

Reprints of articles in this series are not available for distribution, but the articles will be published in book form. The current volume is *Medical Progress Annual 1940* (Springfield, Ill.) no. 3. Charles C. Thomas Company, 1941. \$4.00.

\*Chief, East Surg. Cal. Serv. Co., Massachusetts General Hospital; lecturer in surgery, Harvard Medical School.

septic wounds. Farris's<sup>5</sup> conclusion, based on experiments at the University of Michigan, that cotton causes less reaction in the cornea of the rabbit than other suture materials seems clearly corroborated by clinical data. The sizes most useful are Nos. 30, 40 and 60. It should be used instead of silk for ligatures and interrupted sutures. So-called "quilting cotton" is superior to ordinary cotton thread.

#### WAR WOUNDS

New types of injury to the abdominal viscera have been reported.<sup>6</sup> The term "burst abdomen" is used. One gains the impression that internal injuries without penetration are commoner than in former wars; such injuries are probably caused more frequently by falling debris than by concussion. The majority of abdominal wounds, however, are from fragments of high-explosive shells and are penetrating. The same rules of treatment apply to these injuries as to those seen in civil life. Early intervention (within six hours) gives the best results. Careful débridement, suture of the ruptured hollow viscera and closure without drainage are advocated. Late wounds (over six hours) must usually be regarded as already infected. The use of the Miller-Abbott tube and of the sulfonamides has improved the results. Huge defects of the abdominal wall may be treated by vaseline-gauze packs, to be left in place until extruded by granulation tissue. Vaseline-impregnated canvas may be sutured to the healthy skin edges to cover a large opening in the abdominal wall. The intestines adjust themselves to this new covering and do not become adherent to it. Ogilvie<sup>6</sup> points out that three conditions present in war wounds are not commonly found in the planned abdominal wounds of civil surgery: the abdominal peritoneum is damaged, as well as incised; the number of adhesions is apt to be greatly increased; and the first operation will probably have been done by some other surgeon in another hospital than that in which permanent care is attempted.

In war wounds, the best time to operate is very early (within six hours) or very late (after six weeks). Foreign bodies should not be removed if they are small and not near a large vessel, or if they are not the cause of a urinary, fecal or biliary fistula. The transperitoneal approach should not be employed for the removal of foreign bodies if it can be avoided. Subdiaphragmatic and pelvic abscesses are the only ones needing surgical drainage. Other abscesses either make their way to the surface or are discharged into a hollow viscus. Drainage of abscesses should be delayed as long as possible. Fecal fistulas should be closed very

late unless high in the small intestine. Intestinal obstruction is always treated by a Miller-Abbott tube, and the surgical approaches are identical with those of civil surgery: early operation in small-bowel and late operation in large-bowel obstruction. Care must be exercised to make the anastomosis in a portion of healthy viable bowel. Proximal decompression should always be used in suture of the large bowel.

Gordon-Taylor<sup>7</sup> has described many bizarre abdominal injuries occurring during the bombings of London. The results illustrate the excellent organization and care of the wounded civilians during these raids. Eviscerations and other serious multiple intra-abdominal injuries were successfully treated.

#### APPENDICITIS

Numerous reports have appeared during the past year concerning this common but serious malady. By careful analyses of the results in any clinic, one can lower the morbidity and mortality. The insidious onset and the lack of predominant signs and symptoms account for the serious state in which many of these victims reach the hospital. Educational efforts have been helpful, but there is still much to be desired along these lines.

Faxon and Rogers<sup>8</sup> have dealt with the late cases of appendicitis at the Massachusetts General Hospital. These cases have been separated into two clinical groups: those in which the general peritonitis was unassociated with a mass, and those in which such a mass was present. The data in each group have been carefully studied and allow certain deductions and recommendations that should result in a lower mortality rate. If appendiceal peritonitis is present without a definite mass, operation appears to be most dangerous on the fourth and fifth days of the disease. The McBurney incision seems to be the most satisfactory type. If a mass is present, operation should be deferred, if possible, until after the seventh day, when incision and drainage are done as a primary procedure unless the appendix can easily be removed. If appendectomy is not performed, the patient must return within six weeks for an interval operation.

The routine use of Wangensteen suction in complicated acute appendicitis has long been in practice in the clinic at the Massachusetts General Hospital and many others. Ward,<sup>9</sup> who has recently emphasized this adjunct to successful treatment, reports a reduction in mortality from 5.8 to 3.0 per cent in the cases treated in the University of California Hospital. He points out that decompression by this simple procedure should be carried

out until normal peristalsis and voluntary passage of flatus take place.

Penberthy et al.<sup>10</sup> use the Miller-Abbott tube for this purpose and admit that in two thirds of their cases the tube remained in the stomach, whereas in the other third it was carried into the small intestine. By this method, they have greatly reduced the mortality in children.

Robertson,<sup>11</sup> of Toronto, has had an extraordinarily satisfactory experience with acute appendicitis in children. He attributes his excellent results to early operation provided that the appendix has not perforated. If perforation has occurred, however, operation is withheld until the patient is in good condition. The most important single factor in reducing the mortality in this group of cases is, he believes, the Miller-Abbott tube. He advises immediate use of the tube before obstruction develops.

Proper use of the sulfonamides in appendicitis with spreading infection is established. Without any doubt, this group of drugs is lowering the death rate from appendicitis. Sulfanilamide crystals—4 to 8 gm intra-abdominally and into the wound—give a high blood level within a short time. The less soluble and better tolerated sulfonamides, particularly sulfadiazine, can be used to maintain a satisfactory level for several days. Residual abscesses may occur, but are usually in the pelvis and can be drained at a later time. Drainage at the time of operation should be instituted only when a frank abscess cavity has been opened.

Woodruff and McDonald<sup>12</sup> found 146 cystic tumors of the appendix in 43,000 appendices removed at the Mayo Clinic between 1914 and 1938. Ten of these showed Grade I adenocarcinomas. The rare incidence of cancer in the appendix is interesting in that the ratio is 1:4300 cases.

#### GALL BLADDER AND BILE DUCTS

Early versus delayed operation in acute cholecystitis has continued to be a source of debate among surgeons. In an attempt to settle the matter in our own minds, certain of us<sup>13</sup> at the Massachusetts General Hospital analyzed the data bearing on the subject in a ten-year period. To clarify the terminology used in this argument, we accepted for study only patients with pain, fever, leukocytosis, right-upper quadrant mass or muscle spasm. The surgeon's note describing the gall bladder as acute and the pathologist's report of acute cholecystitis were not accepted without the foregoing criteria. Thus, we rejected the case records of about 100 patients who may have had acute inflammation of the gall bladder but who

were not sufficiently ill to fall into the classification of the serious entity usually suggested by the term "acute cholecystitis." Four hundred and fifteen cases were accepted as fulfilling these requirements. Since gangrene of the gall bladder is necessary to produce rupture and the serious complications increasing the morbidity and mortality, we further analyzed the case records on this basis.

Most of the reports deal with the time interval between admission to the hospital and operation. We believed, as Gage<sup>14</sup> did, that a better understanding of the situation could be determined if the interval between onset of symptoms and operation were regarded as the basis for study. Some of us believed that operation could be done more safely after the acute process had subsided, whereas others, for example, Miller,<sup>15</sup> were of the opinion that early surgery was indicated. This furnished sufficient data to make comparisons of the two schools of thought from our own records. Many interesting facts came to light in this study.

Rarely does a patient under the age of forty-five die following cholecystectomy. Only 2 deaths in 139 cases in this group occurred, and both were due to pulmonary embolism, proved at autopsy.

Only 10 patients had gangrenous gall bladders before the fourth day of the disease, and all recovered; there were only 3 deaths among 108 patients operated on before the fifth day of the disease. Patients operated on after the fifth day of the disease were likelier to have gangrene and perforation, and such cases were associated with a higher morbidity and mortality.

Eighty-five per cent of the patients had been admitted to the hospital during the early period of their illness. Thus, the patient and the physician were not at fault for the delay. Emergency operations in the night, usually carried out under an incorrect diagnosis, resulted in a higher mortality than those done the next morning after proper hydration and so forth.

Free rupture into the peritoneal cavity occurred in only 3 patients, with a fatal outcome in each case.

Cholecystectomy was a safer procedure than cholecystostomy, regardless of the duration of symptoms or the age of the patient. Careful study of the records failed to reveal that removal of the gall bladder would not have reduced the deaths in the group who had simple drainage. In spite of this, we still believe that a drainage operation may, on occasion, be justifiable.

It was not possible, by temperature elevation, degree of leukocytosis or any other evidence, to predict which cases would develop gangrene. One must assume that any acute inflammation of the

gall bladder may develop into gangrene, since 29.4 per cent of these gall bladders were gangrenous at operation.

Our final conclusions are: that the patient with acute cholecystitis should be operated on as soon as the diagnosis is established, fluid balance is restored, and proper operative facilities are at hand; that rarely, if ever, should the operation be considered an emergency; and that the gall bladder should be removed, simple drainage being done only when the circumstances permit a minimum operative procedure.

Berk<sup>16</sup> divided a group of cases into those operated on within forty-eight hours of onset of symptoms and those operated on after this period. The mortality rate in those operated on early was only one fourth that of the late group.

I<sup>17</sup> have previously emphasized the safety factors in gall-bladder surgery. Browne<sup>18</sup> gives further support to the conclusion that careful consideration of the anomalies of the extrahepatic-duct region is essential. In a study of 280 patients at autopsy, he observed that 92.8 per cent had normal common hepatic arteries, with the right hepatic artery passing posterior to the portal vein. Actually, he found a normal left hepatic artery in 66.7 per cent and a normal right hepatic artery in 79.7 per cent of the subjects. In 44 cases, the right hepatic artery closely paralleled the cystic duct. The anomalies of the cystic artery are not so critical from the standpoint of serious damage to the patient during cholecystectomy, but it is interesting to note that one out of three of Browne's subjects had multiple cystic arteries.

The seriousness of an anomalous right hepatic artery, particularly one that crosses anterior to the common hepatic duct, is borne out by a case in which the surgeon left a clamp on a large vessel that proved at autopsy to be the right hepatic artery; the patient succumbed in a manner commonly spoken of as a "liver death." Sutton<sup>19</sup> has produced this syndrome in animals by ligating the right hepatic artery.

Sandrini<sup>20</sup> calls attention to the frequency of anomalies of the cystic duct; such anomalies, in my opinion, account for many of the catastrophes and have some bearing on the mortality rate in gall-bladder surgery. I am sure that "liver death" should be extremely rare and that injuries to the common duct and hepatic arteries will not occur if sufficient care is exercised during the operation.

Pearse<sup>21</sup> has devised and used a vitallium tube for the repair of the common hepatic duct. Clute<sup>22</sup> and McKittrick and I have been able to use this method satisfactorily. Although it is adaptable in

a limited number of situations, it will prove helpful in some anastomoses.

Brackin and David<sup>23</sup> have devised an ingenious type of anastomosis between the biliary system and the gastrointestinal tract. This procedure is believed by the authors, from their experimental and clinical data, to reduce the hazard of stricture and ascending cholangitis following the usual anastomosis. Their technic depends on a necrotizing silk ligature through the undenuded common duct or gall bladder and the mucosa of the stomach or duodenum. This type of anastomosis may be safer from the standpoint of ascending infection, but has the disadvantage of a delay of three or four days in relieving any biliary obstruction that may exist.

#### DUODENAL ULCER

Peters<sup>24</sup> has given a helpful physiologic concept of the proper treatment of certain complications of duodenal and pyloric ulcer. Complete rest of the gastrointestinal tract eliminates vomiting and distention. Without intubation of the stomach and with nothing by mouth, the almost completely constricted pylorus or duodenum allows salivary and stomach secretions to pass. Fluids given under these conditions cause less stimulation and less retention in the stomach if they contain sufficient sodium chloride to make them isotonic with blood serum. This is of great practical value in the preoperative management of obstructing ulcer, and in the postoperative management of any abdominal procedure in preventing ileus and vomiting.

Bisgard and Nye<sup>25</sup> bring out some interesting physiologic data that are opposed to the generally practiced procedures. Gastrointestinal motility is stimulated by the application of ice to the abdominal wall and by the ingestion of hot drinks by mouth. Thus, the ice bag over an inflamed appendix may be harmful. Heat applied to the abdominal wall inhibits gastrointestinal motility, as iced water taken by mouth does. Ice applied externally increases free and total gastric acidity. The ingestion of iced water diminishes the secretion of acid in the stomach. It is further claimed that dipping the patient's hands in iced water produces a stimulation of gastric acidity comparable to that of histamine.

Perforated peptic ulcer has been reviewed by Griswold and Antoncic,<sup>26</sup> and 111 consecutive cases treated in Louisville, Kentucky, were studied; there were 20 deaths in the series. They stress the importance of culturing the free fluid in the abdomen. In 18 cases with positive cultures for streptococci, there were 8 fatalities from peritonitis.

The authors recommend removal of the fluid by suction, closure of the perforation, 5 to 10 gm. of sulfanilamide powder intra-abdominally and 3 to 5 gm. in the wound, silk closure of the wound without drainage and Wangensteen suction. If the culture reveals streptococcus, sulfanilamide therapy is continued.

Ulfelder<sup>27</sup> has reviewed the cases of perforated peptic ulcer for a fifteen-year period at the Massachusetts General Hospital. The results in the last five years have not been better than those in the first five-year period of the study. Most patients surviving operation more than twelve hours after the onset of symptoms were found to have already sealed their perforation. This fact favors the use of the conservative measures of Wangensteen suction and ochsnerization in late cases. The yearly mortality curve roughly parallels the pulmonary infection death rate for Massachusetts.

Williams and Hirtzell<sup>28</sup> offer a suggestion that may prove of great value in the diagnosis of acute perforated ulcer. They state that roentgenograms taken in the left lateral decubitus position show pneumoperitoneum in 88.9 per cent of cases as opposed to 77.7 per cent in the upright position.

Although surgeons have tried a wide variety of operative procedures for the cure of duodenal ulcer, all these methods have been found ultimately unsatisfactory in cases now requiring surgery except a subtotal resection, which includes the entire antrum, as well as a large segment of the fundus. It seems incredible that such an extensive operation should be necessary to relieve a patient suffering from physiologic disease of the digestive tract. This type of attack has long been routine in dealing with hyperthyroidism, yet it is still difficult to consider such radical measures when one is dealing with ulcer. Until a more simple solution is discovered, however, a small percentage of ulcer patients will be, of necessity, subjected to an elimination of the acid-hormone cells of the antrum, as well as a generous share of the acid bearing cells of the fundus. The complications of duodenal ulcer, such as perforation, massive hemorrhage, scar tissue obstruction and persistent symptoms in spite of good treatment, continue to place about 20 per cent of all patients with duodenal ulcer in the hands of the surgeon.

More evidence is being accumulated to substantiate the safety and the excellent end results when a proper partial gastrectomy has been performed on the right patient under ideal conditions. Walters, Lewis and Lemon<sup>29</sup> have reviewed the results in 212 consecutive patients and admit a careful selection for this operation. The operative mortality was 1.9 per cent, and only 2.5 per cent of

patients developed anastomotic ulcers, 83.5 per cent were well on an unrestricted regimen of activity and diet, and 14 per cent required some restriction of diet and activity. The selection of the patient, according to his ability to withstand radical operation, is a significant one in this group of cases. One may assume that the anastomotic ulcers and the small percentage of patients still under some restriction occurred in those cases in which the ideal operation could not be carried out. It is not quite clear but almost certain that the recurrent ulcers developed in patients who either had a small amount of the antrum left in situ or had insufficient fundus removed. One must be sure of a low mortality in these nonmalignant lesions, and a few uncured patients in this group are a sign of better judgment than a higher mortality rate. If one leaves the antrum in subtotal gastrectomy, as advocated by Finsterer,<sup>30</sup> the operation is safer, but one may have to pay for this immediate safety by recurrent ulcers and unrelied patients.

I am in complete accord with McKittrick<sup>31</sup> that, if the operation is technically difficult owing to the extent of the inflammatory reaction about the ulcer, or because of the type of organisms cultured from the ulcer, or if the general condition of the patient is poor, a two stage gastrectomy is justifiable. Certainly, by this method in properly selected cases, there will be a decrease in the morbidity and mortality, both almost invariably associated with difficulties arising from the duodenal stump. The first stage consists in a Finsterer exclusion procedure, and the second stage, six weeks later, in a simple removal of the antrum and pylorus. This period of rest makes the difficult part of the operation easy to do before the reactivation of remaining acid cells has produced an anastomotic ulcer. Doubtless, an occasional patient will develop this complication before the second stage is carried out, but even this is a small price to pay for the added safety of the procedure.

The complications arising from the duodenal stump are well borne out in the excellent paper by McClure and Fallis.<sup>32</sup> Three of the four deaths in their entire series were due to these difficulties. In our own clinic, we know that increased experience of the operator reduces these complications to a minimum, but it is evident that there are technical situations demanding a change of pattern at times. It seems fair to say that a careful survey of the bile ducts, in relation to the ulcer and its inflammatory extension before the decision is made regarding the type of operation planned, will safeguard the outcome more intelligently than any standardized routine procedure.

I have long been interested in denuding the remaining antral segment of its mucosa, as advocated by Bancroft,<sup>33</sup> in difficult cases of duodenal ulcer. At the Massachusetts General Hospital, this procedure has been performed in conjunction with subtotal gastrectomy for duodenal ulcer in 14 cases. Although we have had some difficulties with the thinned-out segment and a few patients have had complications arising from this source, all but one have recovered. In a recent follow-up study<sup>34</sup> of all partial gastrectomies for duodenal ulcer, we were somewhat relieved to find no recurrent or anastomotic ulcers in this small group of cases. Our evidence supports the theory that this procedure is adequate when properly done, but it is definitely a second or third choice with us at present.

The most satisfactory results in our hands have been in cases of duodenal ulcer that has nearly or completely healed by hospital treatment. This may require several weeks and should include, at the end, a week or two of ambulatory activity. Under these circumstances, resection can usually be carried to a point where sufficient normal duodenum can be obtained for an adequate closure. The convalescence is short, and the patient has the greatest chance of taking on his regular duties in life with freedom from discomfort.

#### GASTRIC ULCER AND CANCER

The difficulty in differential diagnosis between benign and malignant ulcers of the stomach has long been recognized. Sufficient emphasis has not been placed on this subject, and many gastric lesions are treated as ulcer until the opportunity for cure is lost. Eusterman<sup>35</sup> believes that the distinction between benign ulcer and carcinoma should be more carefully evaluated in each patient: the larger ulcers—over 2.5 cm. in diameter—may prove malignant, whereas the smaller ones are usually benign, particularly in the younger patient. He advises careful watching of the patient until complete healing takes place, and warns that achlorhydria means cancer. He further states that benign gastric ulcer responds well to medical treatment.

Holman and Sandusky<sup>36</sup> also call attention to the diagnostic error in gastric lesions. In their clinic, the error was 15 per cent when any one diagnostic procedure alone was used. They report a mortality rate of 6.3 per cent in partial gastrectomy for these lesions.

We<sup>37</sup> have analyzed the records of the gastric-ulcer cases at the Massachusetts General Hospital over a ten-year period. It was surprising to find

the diagnostic error as high as 35 per cent. The clinician, the roentgenologist and the gastroscopist preoperatively, as well as the surgeon at the time of operation, were all frequently incorrect in their diagnoses. We studied the acidity on this group and found that patients with "ulcer-cancer" had just as high levels as those with benign ulcer. Acidity was frequently present in typical gastric carcinoma, but achlorhydria was almost pathognomonic of cancer. The age of the patient and the duration of symptoms were important. Patients developing symptoms after forty-five were five times as likely to have cancer as ulcer. Patients of this same age group who had had symptoms over five years were likelier to have ulcer than cancer. The results of partial gastrectomy for ulcer were excellent: only 2 patients in a group of 51 had recurrence of ulcer symptoms. Although the mortality rate for the hospital for radical operation was 6 per cent, we have done forty-two consecutive partial gastrectomies in this ulcer-cancer group, with a single death.

Patients with obvious cancer of the stomach and an operable lesion have a 20 per cent chance of a five-year cure,<sup>38</sup> whereas those resected with the diagnosis of ulcer, but proving to have cancer, have a 40 per cent chance. This seems to be the best argument for early radical surgery in the borderline group.

#### COLON

Gibbon and Hodge<sup>39</sup> have presented another strong appeal for preliminary decompression by cecostomy or colostomy followed by aseptic anastomosis after resection of large-bowel tumors. In a collected group of cases reported by several clinics, the mortality rate was 14 per cent. A comparable series operated on by the exteriorization or obstructive-resection method, commonly called the Mikulicz operation, gave a mortality rate of 27 per cent. Cattell<sup>40</sup> reports from the Lahey Clinic, where the exteriorization operation is routine, a mortality rate of 13 per cent. Thus, in the hands of experts, the two methods have a comparable risk. The morbidity is less in the primary-anastomosis group, and the operability is the same in the hands of experienced surgeons in this field. Either of these satisfactory methods gives better results than open anastomosis in the average case. The latter procedure should be used only after thorough cleansing of the involved bowel by preliminary proximal drainage.

Firor and Poth<sup>41</sup> report on the results of preliminary preparation of bowel lesions with sulfanilylguanidine. Although there is some evidence that

this drug diminishes the number of colonies of pathogenic organisms in the bowel, it is not thought to be of great value by Stone,<sup>42</sup> who has discontinued its use after an experience with 25 cases. The local use of sulfanilamide following large bowel resection seems to be of value.

Toiydzé,<sup>43</sup> by animal experimentation, has shown that thrombosis of venous collaterals due to trauma, infection and postoperative hemorrhage accounts for some of the failures at the suture line in colon anastomosis. I am sure that removal of the fatty appendages preliminary to bowel suture is unwise, and that the anastomosis should be done with these intact and without disturbance of the blood supply to the segment coming through the fatty attachments. At the Massachusetts General Hospital, we have recently encountered an anomalous blood supply to the transverse colon. This has caused us to take into account such a possibility and to modify our usual procedure in midtransverse colonic lesions. If the disease requires removal of the midtransverse colon, the preliminary operation should be anastomosis between the ileum and descending colon, or a cecostomy. Exteriorization of this midsegment, with all the disadvantages of prolonged morbidity and secondary closure, would be justified. We are convinced that anastomosis between the ileum and distal transverse colon followed by extirpation of the entire right bowel at a later date should not be the operation of choice. This method is safe and preferable in all lesions up to the midtransverse colon.

Eggers<sup>44</sup> has reported a group of 82 patients with diverticulitis of the sigmoid whom he has personally observed. 44 per cent developed serious life threatening conditions; 24 per cent had acute perforation with abscess formation or peritonitis with fatal outcome in exactly half of such complications. Five of the 82 cases had associated carcinoma. There were no deaths in a group of 23 patients operated on at a time of election; of 8 who had resection, 2 had associated cancer. The total mortality in the entire group was 20 per cent. Egger's analysis of the symptoms and signs of diverticulitis is of interest, particularly since it shows that approximately 20 per cent of such patients have bleeding.

## REFERENCES

1. Lemmon W. T. A method for contiguous spinal anesthesia. Preliminary report. *Ann Surg* 111:141-144 1940.
2. Haight C. and Ransom H. K. Observations on the prevention and treatment of postoperative atelectasis and bronchopneumonia. *Ann Surg* 114:243-247 1941.
3. Meale W. H. and Ochsenr A. The relative value of cargut silk, linen and cotton as suture materials. *Surgery* 7:485-514 1940.
4. Meale W. H. and Long C. H. The use of cotton as a suture material with particular reference to its clinical application. *J A M A* 117:7140-7143 1941.
5. Farris J. M. Tissue reactions to suture materials: a preliminary report. *Ann Surg* 114:159 1941.
6. Ogilvie W. H. The late complications of abdominal war wounds. *Lancet* 2:253-256 1940.
7. Gordon Taylor G. Unpublished data.
8. Faxon H. H. and Rogers H. Appendiceal peritonitis: a statistical study of six hundred and seventy-one cases. *New Eng J Med* (in press).
9. Ward R. Appendicitis with complications: a reduction in mortality due to the use of continuous gastro-intestinal decompression. *West J Surg* 48:1-4 1940.
10. Penberthy G. C., Noer P. J. and Benson C. D. The treatment of adynamic ileus by gastro-intestinal intubation in children. *Surg Gynec & Obst* 71:211-21 1940.
11. Robertson D. E. Unpublished data.
12. Woodruff R. and McDonald J. R. Benign and malignant cystic tumors of the appendix. *Surg Gynec & Obst* 71:50-55 1940.
13. Allen A. W. and Wallace R. H. Acute cholecystitis. *Arch Surg* 43:76-7 1941.
14. Gage M. Surgery of acute cholecystitis. *New Orleans M & S J* 91:70-620 1939.
15. Miller R. H. Acute cholecystitis. *Ann Surg* 92:644-648 1930.
16. Berk J. E. The management of acute cholecystitis. *Am J Digest Dis* 7:325-337 1940.
17. Allen A. W. The surgical management of the usual extrahepatic biliary lesions. *Surgery* 8:188-203 1940.
18. Browne F. J. Viridans origin and course of the hepatic artery and its branches. *Surgery* 8:424-445 1940.
19. Sutton J. F. Jr. Acute postoperative necrosis of the liver. *Am J M S* 192:219-274 1936.
20. Sindriani G. Anatomie congenita delle vie biliari (abstracted by Michel Debikay). *Internat Abstr Surg* 71:767 1940.
21. Pearce H. E. Benign stricture of the bile ducts treated with a vitallium tube. *Surg* 10:37-44 1941.
22. Clute H. M. Bile duct reconstruction with a vitallium tube. *New Eng J Med* (in press).
23. Brack N. R. and Davil V. C. Anastomosis of the bile ducts to the gastro-intestinal tract by a method of transfixion necrosing suture. *Ann Surg* 114:616-634 1941.
24. Peters J. P. The structure of the blood in relation to surgical problems. *Ann Surg* 112:490-497 1940.
25. Disgard J. D. and Nye D. The influence of hot and cold applications upon gastric and intestinal motor activity. *Surg Gynec & Obst* 71:172-180 1940.
26. Griswold R. A. and Antoniec R. F. Perforated peptic ulcer. *Ann Surg* 113:791-801 1941.
27. Ulfelder H. Unpublished data.
28. Williams A. J. and Hartzell H. V. Perforated peptic ulcer: a more accurate method of roentgen diagnosis. *Surg Gynec & Obst* 71:606-614 1940.
29. Walters W. Lewis E. B. and Lemon R. G. Primary partial gastrectomy (Pólya type) for duodenal ulcer: a study of results in 212 cases. *Surg Gynec & Obst* 71:240-243 1940.
30. Finsterer H. and Cunha F. The surgical treatment of duodenal ulcer. *Surg Gynec & Obst* 52:1099-1114 1931.
31. McKittrick L. S. Personal communications.
32. McClure R. D. and Fallis L. S. Partial gastrectomy for peptic ulcer: a review of seventy-four operations. *Surgery* 8:575-586 1940.
33. Banrott F. W. Modification of Devine operation for pyloric exclusion of duodenal ulcer. *Am J Surg* 16:223-230 1932.
34. Allen A. W. and Welch C. E. Gastric ulcer: the significance of this diagnosis and its relationship to cancer. *Ann Surg* 114:498-509 1941.
35. Eusterman G. B. Small carcinomatous gastric lesions simulating chronic benign ulcer: present status of differential diagnosis and treatment. *Minnesota Med* 23:709 1940.
36. Holman C. W. and Sandusky W. R. Further observations on the diagnosis and treatment of gastric lesions. *Ann Surg* 112:339-343 1940.
37. Allen A. W. and Welch C. E. Gastric resection for duodenal ulcer: follow-up studies. *Ann Surg* (in press).
38. Parsons L. and Welch C. E. The curability of carcinoma of the stomach. *Surgery* 6:327-338 1939.
39. Gibbon J. H. Jr. and Hodge C. C. Aseptic immediate anastomosis following resection of the colon for carcinoma. *Ann Surg* 114:635-652 1941.
40. Castle R. B. Discussion of Gibbon and Hodge.<sup>39</sup>
41. Furr W. M. and Poth E. J. Intestinal antiseptic with special reference to sulfanilylguanidine. *Ann Surg* 114:663-671 1941.
42. Stone H. B. Discussion of Furr and Poth.<sup>41</sup>
43. Toiydzé S. S. Ligation and thrombosis of veins of large intestine. *Internat Abstr Surg* 72:255-256 1941.
44. Eggers C. Acute diverticulitis and sigmoiditis. *Ann Surg* 113:15-29 1941.



## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTE-MORTEM AND POST-MORTEM RECORDS AS USED  
IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

### CASE 28021

#### PRESENTATION OF CASE

A fifty-four-year-old Irish teamster was admitted to the hospital because of hoarseness and difficulty in swallowing.

He was well until about seven weeks before entry, when he became aware of hoarseness, unassociated with other symptoms. This persisted and grew progressively worse. Two weeks before entry, he first noted difficulty in swallowing solid foods: pieces that he swallowed lodged at the level of the larynx, requiring manipulation of the trachea to make them pass. This dysphagia grew worse, although the patient had no trouble in swallowing liquids. His diet was therefore limited to fluids. At about the same time, there was onset of a tickling sensation in the throat, leading to repeated dry coughing. After a while, the cough became productive of yellow-brown sputum. During the last two weeks, dyspnea appeared, at first only on exertion, but later at rest as well. In the two nights preceding entry, the patient was kept awake by dyspnea and orthopnea. He noted that the "choking" spells occurred especially when he lay on his right side. During the night before entry, he coughed up bright-red blood three times, to a total amount of about five tablespoonfuls. There was a loss of considerable weight during his illness, although the appetite remained good.

The past and family histories were irrelevant.

On admission, the patient appeared about ten years older than his actual age; he was well developed and nourished, despite recent weight loss. He was florid faced, with poor visual acuity and sclerotic fundi. The teeth were carious. The trachea was deviated markedly to the right. The chest was barrel shaped. Respirations were slightly labored, with "leopard-growl" sounds and rhonchi transmitted throughout both lungs. The heart was within normal limits of size, with somewhat distant sounds. The abdomen was soft, with the liver palpable on deep inspiration. The prostate gland felt enlarged, but smooth and of average consistence.

The temperature was 100°F., the pulse 80, and the respirations 25. The blood pressure was 170 systolic, 100 diastolic.

Examination of the blood showed a red-cell count of 3,460,000 with 8.5 gm. hemoglobin, and a white-cell count of 9000 with 72 per cent polymorphonuclears. The blood Hinton reaction was negative. The serum protein was 6.5 gm. per 100 cc., the chlorides 97.4 milliequiv. per liter, and the vitamin C level 0.1 mg. per 100 cc. The urine was normal.

Roentgenograms of the chest showed incomplete collapse of the right lower lobe, with apparently dilated bronchi included in the lobe. The middle lobe was likewise decreased in size. The mediastinum was displaced slightly to the right, and showed marked inspiratory shift toward the right. A soft-tissue mass 5 cm. in diameter occupied the left upper mediastinum and seemed to involve the wall of the esophagus. Just below the crossing of the aorta, there was another defect on the left anterior wall of the esophagus, with no definitely visible soft-tissue mass. There was slight delay in the flow of barium in the region of the upper mediastinal mass, but no delay was observed in the region of the lower esophageal defect. The patient had difficulty in emptying the barium from his pharynx, and at times a small amount of barium was seen in the trachea.

The temperature fluctuated irregularly from 100 to 103°F. The patient was given glucose clyses and various vitamins. On the seventh hospital day, a bronchoscopy was performed. The left vocal cord moved partially on phonation, but was well abducted. The right vocal cord was partially paralyzed in the midline. Airway through the larynx was satisfactory. Just below the glottis, a mass of apparent tumor tissue was found arising from the left lateral and posterior walls of the trachea and occluding about two thirds to three fourths of the lumen. The bronchoscope was then passed distal to the tracheal growth, and the right bronchial tree hastily examined. It appeared only slightly narrowed in the region of the right middle and lower lobes, and no outcropping could be seen. Since it was obvious that tracheal obstruction might occur following removal of the bronchoscope, a tracheotomy was performed with the bronchoscope in place. A tracheotomy cannula was then introduced, under novocain anesthesia, as low in the midline as possible. The patient returned to the ward in good condition.

The following morning, he was fairly comfortable; during the afternoon, however, he developed increasing respiratory distress and, in spite of frequent suction performed by a special nurse, died early that evening.

## DIFFERENTIAL DIAGNOSIS

DR. LOWREY F. DAVENPORT: May we see the x-ray films?

DR. RICHARD SCHATZKI: This triangular shadow in the right cardiophrenic angle was interpreted as a lower lobe that had markedly decreased in size or was collapsed. A film with more exposure shows what appear to be dilated bronchi in this area. The septum between the upper and middle lobe is lower than normal, and in the lateral view one sees the middle lobe also somewhat decreased in size. A lesion producing the obstruction to the bronchi of the lower and middle lobes is not visible. There is, however, this mass in the mediastinum, which displaces the trachea to the right side. During fluoroscopy, the esophageal lesions described in the record were by no means so obvious as they sound in the finished report. This patient apparently had only slight difficulty in swallowing the barium. He complained of some obstruction in the region of the upper esophageal lesion in the area of the soft-tissue mass, where the trachea was pushed over to the right side and forward. The trachea is very poorly visible in this region, a fact that is adequately explained by the bronchoscopic findings. The lower esophageal lesion just below the bifurcation was even less conspicuous. There was not the slightest impairment of the passage of barium by this lesion, which could be demonstrated only when the film was taken at the moment when the barium passed by the lesion. To sum up, there were three lesions present: two involving the esophagus, and one involving the right lower and middle lobes.

DR. DAVENPORT: We are given definite information that the man had a tumor in his trachea, and we gain the additional evidence from the x-ray films that he had a tumor in his esophageal wall, and also evidence of obstruction to the bronchus of the right lower lobe; I think the only questions that need concern us are the nature of the tumor and where it arose. On a percentage basis, both cancer of the lung and cancer of the esophagus appear much more frequently in men than in women—the ratios are put as high as 10:1. Consequently, we get no particular lead there. The onset of the inspiratory symptoms and the onset of dysphagia were almost simultaneous. It is not unusual in extensive cancer of the esophagus for dysphagia to be a late manifestation, and we have seen cases with involvement of almost the entire length of the esophagus without any complaint of difficulty in swallowing until the terminal stage. We have the report from the bronchoscopy that no tumor was visible in the lower bronchial tree.

The tumor was high in the trachea, an unusual location for a primary cancer. Both benign and malignant tumors of the trachea are very rare, and I think from the information that we are safe in assuming that the growth was primary in the esophagus and that all the respiratory difficulties were the result of secondary involvement of the trachea, which is not an uncommon complication of the late stages of cancer of the esophagus.

The symptoms of the last few days, such as the acute dyspnea on change of position, suggest that there was actually a communication—a direct fistula—between the esophagus and trachea, with intermittent leakage of material from the esophagus into the trachea at times. Paralysis of the vocal cords too, on a percentage basis, is not an uncommon late complication of esophageal cancer. The bronchial narrowing in the right lower lobe might have been due to pressure from metastases or from the lower portion of the esophageal tumor.

We certainly do not have to consider benign growths or tumor arising from any other structure in that region. I should exclude a primary growth in the thyroid gland or any other structure.

My diagnosis is primary cancer of the esophagus, with all the subsequent manifestations due to involvement by both direct extension and pressure.

DR. TRACY B. MALLORY: Do you want to give your interpretation of the x-ray examination, Dr. Schatzki?

DR. SCHATZKI: I had the same difficulty that Dr. Davenport had in explaining how to connect these three lesions. I was impressed by the fact that this patient's first symptom was not difficulty in swallowing. I think it is extremely rare for a patient with cancer of the esophagus to report to a physician with any other complaint than difficulty in swallowing. Having seen several cases of cancer of the bronchus involving the esophagus secondarily and none of cancer of the lower esophagus involving the trachea secondarily, although having seen quite a few with lesions higher up that involved the trachea, I thought it was a little more likely that the primary lesion was in the bronchus and that the masses in the mediastinum were metastases; I knew that this was not much better than a guess, but I definitely believed that I had to connect all these three lesions in some way.

DR. EDWARD F. BLAND: Does the small amount of barium in the trachea mean obstruction in the esophagus?

DR. SCHATZKI: My impression was that it spilled over into the larynx because the patient had partial paralysis of the pharynx.

DR. BLAND: You did not think it evidence of a fistula at that time?

DR. SCHATZKI: No.

DR. ALLEN G. BRAILEY: How does Dr. Davenport explain the collapsed lower lung?

DR. DAVENPORT: By pressure.

DR. BRAILEY: From where? The main mass of the tumor was higher up.

DR. DAVENPORT: The patient had extensive neoplastic disease throughout the mediastinum. The whole question was where it arose. Was it primary in the respiratory tract or in the gastrointestinal tract?

DR. MALLORY: Certainly, one of the unusual features of this case is the nearly simultaneous appearance of difficulty in swallowing and difficulty in breathing.

DR. EDWARD B. BENEDICT: I saw the patient and was more impressed with the difficulty in swallowing than with hoarseness, and I should have esophagoscoped him rather than bronchoscoped him except that I was afraid of causing complete tracheal obstruction by pressure of the esophagoscope. Accordingly, I bronchoscoped him.

#### CLINICAL DIAGNOSES

Bronchiogenic carcinoma, with metastases to trachea and esophagus.

Bronchopneumonia.

#### DR. DAVENPORT'S DIAGNOSIS

Carcinoma of the esophagus, with secondary tracheal extension.

#### ANATOMICAL DIAGNOSES

Carcinoma of the esophagus, with metastasis to a mediastinal lymph node resulting in extension into the trachea and esophagus and an esophagotracheal fistula.

Bronchiectasis, chronic: right middle and lower lobes.

Acute tracheobronchitis.

Endocarditis, chronic rheumatic: aortic and mitral valves.

#### PATHOLOGICAL DISCUSSION

DR. MALLORY: Post-mortem examination showed a tumor mass, the major part of which lay between the trachea and esophagus and had spread into each of these structures secondarily. A fistulous tract connecting the esophagus and trachea had developed through the tumor. It was quite clear, however, that the tumor was not primary in either of these tubular structures at that point, whereas the second point of obstruction lower down in the esophagus, which Dr. Schatzki demonstrated, did present the characteristic picture of

primary cancer of the esophagus. A metastasis in a lymph node high in the mediastinum had extended both anteriorly and posteriorly, producing essentially all the symptoms. I doubt if the primary tumor caused any of them. The right middle and lower lobes showed very extensive and old bronchiectasis, with fibrous pneumonitis. The bronchi showed no points of narrowing, and despite the lack of any history of bronchiectasis, the lesion obviously antedated the carcinoma by many years. It is not surprising that the coincidence misled Dr. Schatzki. There was also rheumatic heart disease.

#### CASE 28022

#### PRESENTATION OF CASE

A sixty-two-year-old housewife was admitted to the hospital because of severe dyspnea.

She was in good health for many years, except for extreme obesity. About one week before entry, she began to complain of shortness of breath accompanied by cough, but no other symptoms. Four and a half hours before entry, there was sudden appearance of substernal pain, following the emotional shock of hearing war news. This pain persisted, and was soon followed by severe, increasing dyspnea and by a cough that was productive of white sputum.

The past history was irrelevant, except for a suspicion that the patient had had "high blood pressure" for some time. The family history was noncontributory.

Physical examination showed an obese, moribund woman weighing about 350 pounds whose skin was pallid, slightly cyanotic and moist from perspiration. She was comatose, and the heart sounds could not be heard. The respirations were irregular, 8 to 10 per minute, with coarse bubbling rales. The temperature was not recorded. The pulse and blood pressure could not be obtained. There was no peripheral edema.

Oxygen was administered by a Boothby mask, tourniquets were applied, and intracardiac Coramine and adrenalin were given, without effect. Death occurred fifteen minutes after entry.

#### DIFFERENTIAL DIAGNOSIS

DR. JOHN TALBOTT: The story is brief, and the clinical picture appears to be uncomplicated. The patient had no complaints until a week before death. She was obese, and was said to have had hypertension, but neither of these suggest an impending rapid exitus. One week before death, the patient had some dyspnea and a cough productive of white sputum. Presumably these were not incapacitating, and no mention is made of her seek-

ing medical advice. Five hours before death, the patient was stricken with substernal pain and severe dyspnea. She was brought to the hospital moribund. The heart sounds were inaudible, the pulse and blood pressure could not be obtained, and the lungs contained moist rales. These were all the data available, and from them we must explain the sudden death.

Massive pulmonary infarction is a possibility. If this were the correct explanation, there should be something to suggest a focus for emboli. A deep infection of the veins of the abdomen and legs is the commonest cause of pulmonary emboli. I have excluded a phlebitis because there are no grounds for suspecting it. Furthermore, the patient did not have chronic valvular heart disease and no mention is made of auricular fibrillation. It is possible that the dyspnea present during the week preceding death might have been caused by small pulmonary emboli. I have excluded pulmonary embolism, finally, because of the statement that the cyanosis was mild. A patient dying from massive pulmonary embolism is apt to be deeply cyanotic.

A dissecting aneurysm might produce a sudden death such as this, but I am disinclined to consider it seriously. There is no history of back or leg pain—merely the hypertension and sudden death.

An acute episode of myocardial anoxia seems most probable. The absence of symptoms of angina in the past does not argue against this diagnosis. It is appreciated that the first symptom of coronary occlusion may appear only a few hours before death. It is granted that coronary occlusion is less common in women than it is in men; however, the obesity and hypertension seem to counterbalance her sex. The story of dyspnea during the week before death is consistent with coronary insufficiency. In acute insufficiency, vasomotor shock is profound. This was evident from the pallid skin, slight cyanosis, sweating and failure to detect any pulse or blood pressure. Of course, the failure to hear heart sounds might have been related to the abundance of subcutaneous fat, but it was more likely because of their weak character.

The lack of laboratory data allows us to speculate what such data might have shown. No mention is made of venous distention, so that the venous pressure was presumably not elevated, as it might have been in pulmonary embolism. An electrocardiogram would have been of interest in providing information regarding a previous coronary occlusion or in detecting a cardiac arrhythmia terminally. It would have been less informative

concerning the terminal episode. A urine sample was not obtained, but we have no evidence to suggest a vascular nephritis. An x-ray film of the chest would have helped to determine the size of the heart and the presence or absence of a primary pulmonary process.

With the meager evidence available, I shall rest my argument on the most probable diagnosis: coronary insufficiency. It is possible that anatomic changes in the myocardial muscle accounted for the dyspnea before the terminal event.

#### CLINICAL DIAGNOSES

Coronary thrombosis.

Pulmonary edema.

#### DR. TALBOTT'S DIAGNOSES

Coronary sclerosis and coronary occlusion.

Old myocardial infarction.

#### ANATOMICAL DIAGNOSES

Pulmonary embolism and thrombosis.

Obesity, extreme.

Hypertrophy of the heart.

Carcinoma of the tail of the pancreas.

Cholecystitis, chronic.

Cholelithiasis.

Cortical adenoma of the adrenal gland.

Pheochromocytoma of the adrenal gland.

Congenital anomaly: bifid ureter and double renal pelvis, left.

Adenoma of kidney.

Endometrial polyp.

Endocervical polyp.

Leiomyoma uteri.

Miliary tuberculosis, healed, of spleen and liver.

#### PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: Dr. Talbott wisely stuck to the only point that could profitably be discussed in regard to this patient: the cause of her sudden death. He quickly narrowed the question down to two possibilities: pulmonary embolism and coronary disease. He placed his bet, as the clinicians on the wards did, on coronary thrombosis. We found, however, essentially normal coronary arteries and multiple pulmonary emboli. The main pulmonary trunk was empty as far as the point of bifurcation, but both the right and left pulmonary arteries were almost completely filled with fresh thrombi, which could be traced along all their branches down to the smallest grossly recognizable vessels of each lung. Imbedded in the matrix of these fresh thrombi were numerous darker brownish-red, twisted and coiled fragments of emboli, ranging from 3 to 6 mm. in

diameter. It seems quite clear that there had been multiple small emboli and then secondary thrombosis, which had virtually completely blocked the entire pulmonary arterial tree. We did not search for the source of the emboli, because a dissection of the vascular tree of the massive nether extremities threatened to produce insuperable difficulties for the embalmer.

The heart was large, weighing 500 gm., but there were extensive subendocardial fat deposits that must have weighed 75 gm. Discounting this, the heart was probably not greatly disproportionate to the size of the body. A few patches of atheroma were found in the coronary branches, but nowhere was there significant narrowing of the lumens.

*Entirely aside from these factors, which were responsible for her death, the patient proved to be a museum of pathological curiosities. One always suspects endocrinopathy when dealing with extreme obesity. The pituitary and thyroid glands were both normal. The parathyroid glands were unusually large, but this proved to be due merely to exceptional amounts of interstitial adipose tis-*

sue, and the actual parathyroid tissue was, if anything, atrophic. One adrenal gland showed a cortical adenoma nearly 2 cm. in diameter, and the other showed a small but distinct pheochromocytoma of the medulla. There were a cortical adenoma of the kidney, endometrial and cervical polyps and multiple fibroids. The adenoma of the adrenal gland was not large enough to suggest a Cushing's syndrome, and there was nothing else to substantiate it, such as masculinization, vascular nephritis or increase in the basophilic cells of the pituitary gland. On the law of averages, one might have guessed that a woman of her configuration would have had gallstones. We found many of them enclosed in an enlarged gall bladder with thickened walls. A final total surprise was an early carcinoma of the tail of the pancreas, about 2 cm. in diameter. This was clearly of the acinar type, and consequently cannot be considered to have been a factor in her death. Two final items for the catalogue were the presence of many inactive fibrotic, almost healed, but recognizable miliary tubercles in the liver and spleen, and a congenital anomaly of the urinary tract.

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established in 1828

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND  
PUBLISHED UNDER THE JURISDICTION OF THE COMMITTEE  
ON PUBLICATIONS

Official Organ of  
THE MASSACHUSETTS MEDICAL SOCIETY  
and  
THE NEW HAMPSHIRE MEDICAL SOCIETY

## EDITORIAL BOARD

Joseph Garland M.D.	Stephen Rushmore M.D.
William B. Breed M.D.	Henry R. Viets M.D.
George R. Minot, M.D.	Robert M. Green M.D.
Frank H. Lahey M.D.	Charles G. Lund M.D.
Shields Warren, M.D.	John F. Fulton M.D.
George L. Tobey Jr., M.D.	A. Warren Searles M.D.
C. Guy Lane M.D.	Dwight O'Hara M.D.
William A. Rogers M.D.	Chester S. Keefer M.D.

## ASSOCIATE EDITORS

Thomas H. Lanman M.D.	Donald Munro M.D.
Henry Jackson Jr. M.D.	

Walter P. Bowers M.D., EDITOR EMERITUS  
Robert N. Nye M.D., MANAGING EDITOR  
Clara D. Davies ASSISTANT EDITOR

SUBSCRIPTION TERMS \$6.00 per year in advance postage paid for the  
United States, Canada, \$7.04 per year, Boston funds \$8.52 per year for all  
foreign countries belonging to the Postal Union

MATERIAL for early publication should be received not later than noon  
on Friday

THIS JOURNAL does not hold itself responsible for statements made by any  
contributor

COMMUNICATIONS should be addressed to the *New England Journal of  
Medicine*, 8 Fenway Boston Massachusetts

## SERVICES FOR THE CARE OF CIVILIAN CASUALTIES

MASSACHUSETTS was one of the first states to set up adequate plans for the protection and medical care of the civilian population in the event of military attack, and a handbook, *Organization Medical Division and Care of Injured Civilians*, was published by the Medical Division of the Massachusetts Committee on Public Safety in September, 1941. Since then, many changes in organization have necessitated a second and revised edition that appears, in full, in this issue of the *Journal*, under the title, "Organization of Emergency Services for the Care of Civilian Casualties." The present recommendations bear the approval, in principle, of the defense councils of the five other New England states and of the American Na-

tional Red Cross. The text will be issued as a handbook, which may be obtained by application to the Massachusetts Committee on Public Safety; furthermore, additions revised to conform with conditions in some of the other New England states will be made available by their respective defense councils.

The essential points of the plan call for a central state committee with regional medical heads, who assist in the formation of local organizations. Each community has a medical committee, comprising representatives of the professions and agencies concerned with all phases of medical care. Furthermore, each community has a chief medical officer, who is responsible for *all* aspects of emergency medical care, including the organization and equipment of first-aid parties and medical first aid posts and the establishment of ambulance services, of a medical depot or depots, of casualty stations and of hospital services. In times of emergency, the chief medical officer proceeds to the report center and orders the mobile medical units—first-aid parties, medical first aid posts and ambulances—to the medical depot, and if an incident occurs, he sends these units to the site of disaster. He is also responsible for the direction of the walking wounded to medical first-aid posts or casualty stations and for the transportation by ambulance of the more seriously wounded to the hospitals organized for emergency care. Subsequent transfer of the casualties to base hospitals is a responsibility of the regional medical head, and the evacuation of those who reside in particularly dangerous areas or who are especially vulnerable to disaster—women, children, the infirm and handicapped and the aged—is carried out under the supervision of the Evacuation Division. It is emphasized that the general scheme is not rigid and that the program suitable for a rural community is necessarily different from that in a metropolitan area.

All hospitals are organizing their staffs in such a way that twenty-four-hour emergency service can be provided. In the large urban hospitals, operating teams whose members are well trained in the care of certain types of injury—for ex-

ample, burns, fractures, shock, chest injuries, facillo-maxillary injuries and so forth — are being formed. In no instance, however, has a member of the permanent hospital staff been assigned to a medical first-aid post, for in times of emergency, all staff members will be needed at the hospital.

The many local chapters of the American Red Cross are taking an extremely active part in the program. They are supplying the surgical dressings in the first-aid kit belts of the first-aid parties; they will provide and administer mobile canteens and will furnish many of the ambulances, all of which are under the direction of the chief medical officer; and they will also arrange for the temporary housing, clothing and feeding of uninjured refugees.

All in all, Massachusetts and the other New England states should be proud of the initiative and the accomplishments of the state defense councils, of the medical, dental and nursing professions and of relief agencies in providing a comprehensive and unified scheme for the care of civilian casualties.

---

## THE HUNTINGTON HOSPITAL

THE Collis P. Huntington Memorial Hospital, founded in 1912 as the hospital of the Harvard Cancer Commission, closed December 31. Fortunately, its patients will be cared for at the new Huntington Clinic at the Massachusetts General Hospital. Furthermore, the medical research laboratories, under the direction of Dr. Joseph C. Aub, have been given a generous amount of space at the Massachusetts General Hospital, and as soon as details can be arranged, the attack on the problems of growth, normal and abnormal, will be continued. The State Tumor Diagnosis Service, long maintained at the Huntington Hospital, will continue work in its present laboratories, without interruption.

As an indication of the advance that New England has made in the fight against cancer, the closing of the Huntington Hospital will mean the loss of less than 8 per cent of the beds for cancer patients, whereas fifteen years ago it would

have meant the elimination of all such beds, other than a few for terminal care. Although the Massachusetts General Hospital will provide some additional beds for cancer cases, this does not mean that the situation can be regarded complacently and that special effort must not be made to compensate for the phases of work carried on at the Huntington Hospital that have been discontinued or will be cut down.

The Huntington Hospital was the scientific parent of the Pondville Hospital at Norfolk, the cancer unit of the Westfield State Sanatorium, the Palmer Memorial Hospital — the cancer unit of the New England Deaconess Hospital — and the state-wide tumor clinics, of which Massachusetts can justly be proud. Furthermore, many of the men specially skilled in cancer therapy received their training there. Those who served as student house officers, residents and members of the staff have made good use of the knowledge gained in the wards and clinics, returning to the community many times the value of the resources given to the hospital.

Under the leadership of the late Dr. Robert B. Greenough, the hospital reached its peak of influence. His views, largely based on experience gained there, shaped to a considerable degree the course that programs aimed at the control and treatment of cancer have since followed. But the day of the small special hospital has passed. Too costly in these times to operate for the number of patients it can serve, and its place in large part taken by special provisions in the large general hospitals, it can live only if heavily endowed.

In the management of the Huntington Hospital, another factor entered. It was operated by Harvard University, an educational institution, not a hospital corporation concerned with supporting itself by income from patients. Faced with continuing deficits at the hospital and with a problem not properly within its field, the university has wisely decided to transfer the care of patients to the Massachusetts General Hospital.

The research activities of the Harvard Cancer Commission will continue. The discoveries of the past — such as the fundamental observation by

Tyzzar of the inheritance of tumor susceptibility in animals, the development of the radium emanation plant and the use of radon by Duane, the advances in knowledge of the relations of hormones to normal and abnormal growth and the isolation of growth inhibitors by Aub and his associates and the demonstration of individual human susceptibility to cancer by Warren's studies—augur well for progress in the future.

It is heartening to know not only that the research activities under Dr. Aub will be continued but that the clinical work, done so soundly and for so many years by Dr. Channing C. Simmons and the staff, will be carried on at the Massachusetts General Hospital, even though the hospital and its clinical staff have been discontinued. Hospitals, like human beings, die, but their good is not "interred with their bones."

## MEDICAL EPONYM

### LUGOL'S SOLUTION

This was described by J. G. A. Lugol (1786-1851), physician at the Hospital Saint Louis, in "Mémoire sur l'emploi de l'iode dans les maladies scrofuleuses [A Note on the Use of Iodine in Scrofulous Diseases]," which was read before the Royal Academy of Sciences at the session of June 22, 1829, and published at Paris by J. B. Baillière in the same year. The following is a translation of sentences on pages 48 and 49:

The method of preparation that I regard as most reliable is that of complete solution in distilled water . . . the amount of which vehicle I have established as one pound I then dissolve one half a grain, two thirds of a grain or one grain of iodine, to have three concentrations of this remedy at my disposal . . . Furthermore, I have sought to make this solution digestible by adding twelve grains of sodium chloride . . . I have termed the three concentrations of this solution, *iodized mineral water* No 1, No 2 and No 3

R. W. B

## MASSACHUSETTS MEDICAL SOCIETY

### COMMITTEE ON MATERNAL WELFARE

#### ANALYSIS OF CAUSES OF MATERNAL DEATH IN MASSACHUSETTS DURING 1940

During 1940, in Massachusetts, 219 maternal deaths were reviewed by the Section of Obstetrics

and Gynecology. The various causes of death are shown in Table 1; 2 deaths of nonpuerperal origin are included. It is very gratifying that there was a further decrease in the maternal-mortality rate: in 1939, it was 3.4 per 1000 living births, and in 1940, it was 2.8. The most striking reduction was

TABLE 1 Causes of Maternal Death.

CAUSE	NO OF DEATHS
Sepsis including abortions	48
Medical (pneumonia cardiac disease chronic nephritis and so forth)	43
Embolism	28
Hemorrhage including separated placenta and placenta previa	27
Alluminaria and eclampsia including toxemia	25
Surgical	13
Anesthesia	7
Ectopic pregnancy	3
Transfusion	8
Shock	2
Perinicious vomiting	2
Mesenteric thrombosis	2
Rupture of uterus	9
Nonpuerperal	2
Total	219

in the deaths from sepsis. in 1939, of 253 maternal deaths investigated, 74 were due to sepsis, but in 1940, only 48 were from that cause. It is very likely that chemotherapy was responsible for this improvement.

In this and subsequent issues of the *Journal*, the various cases will be analyzed briefly under their individual classifications. It must be borne in mind that many cases may be classified under one heading as well as another. For example, in an operative case in which version had been performed and in which the uterus had been ruptured, resulting in peritonitis, the death might be classified by one person as due to sepsis and by another as caused by a ruptured uterus. But an attempt has been made to classify all these deaths under the heading that seems to have been the primary cause.

### SEPSIS

Of the total number of cases classified as due to sepsis, the astounding number of 23 were caused by criminal or self-induced abortions. The state of Massachusetts would have had a remarkable record if these were not included. Seventeen of the 23 were cases investigated by the medical examiner, but in only 5 was an autopsy performed. The large number of criminal abortions simply emphasizes the serious step that any woman takes who attempts to interfere with a pregnancy that she does not want.

The deaths from cesarean section will be discussed in Dr. DeNormandie's résumé. It is in-



teresting to note that the Waters operation does not always ensure a successful outcome, since 1 patient in whom a Waters had been performed died of general sepsis.

Only 12 cases of sepsis following pelvic delivery were reported. Some of these cases were treated with chemotherapy, which again shows that, although this method of therapy has played an important part in the lowering of maternal deaths due to sepsis, it is not 100 per cent successful.

The review of the patients dying from sepsis leaves one much encouraged, particularly because injudicious operation as a contributing cause of infection was absent. The section has tried to teach conservatism, since it is well known that the more conservative obstetrics is practiced, the less will bungling operation result, with its accompanying infection.

Sepsis as a cause of maternal mortality can be lowered only by a rigorous crusade against the criminal abortionist, by a diminution in the number of cesarean sections done when the indication is not justified, by a continued emphasis on conservatism in all obstetrics, and by earlier recognition of the specific etiology of any infected case so that proper and adequate chemotherapy may be instituted immediately.

## WAR ACTIVITIES

### CIVILIAN DEFENSE

#### Medical Handbook No. 2

#### Organization of Emergency Services for the Care of Civilian Casualties\*

PREPARED BY THE MEDICAL DIVISION OF THE MASSACHUSETTS COMMITTEE ON PUBLIC SAFETY AND APPROVED, IN PRINCIPLE, BY THE STATE DEFENSE COUNCILS OF MAINE, NEW HAMPSHIRE, VERMONT, RHODE ISLAND AND CONNECTICUT AND BY THE AMERICAN NATIONAL RED CROSS

1. AIM AND PURPOSE. This handbook outlines a plan for the organization of emergency services for the care of civilian casualties in the event of an enemy attack, which would most probably come in the form of an air raid or sabotage. It also standardizes the medical equipment and personnel necessary for the care of such casualties from the time of injury through convalescence. The plan is flexible and can be adapted to a densely populated metropolitan area or to a rural community.

2. ORGANIZATION OF THE MEDICAL DIVISION. The general organization of the Medical Division of the Massachusetts Committee on Public Safety is shown in Fig. 1.

\*This handbook is a revised edition of *Medical Handbook No. 1 Organization Medical Division and Care of Injured Civilians*, published by the Medical Division, Massachusetts Committee on Public Safety. The information concerning organization and equipment supersedes that contained in the previous edition.

It is headed by a medical director† (and deputy medical director), who is chairman of a central executive committee, which is assisted by various central subcommittees (Fig. 2). Working in conjunction with the director are the regional medical heads, corresponding in number and location to regions (so-called "districts" in publications of the Office of Civilian Defense) specified by the United States Army. They are assisted by deputy regional medical heads. In Massachusetts, there are nine regions (Fig. 3), nine regional medical heads (Fig. 2) and eighteen deputy heads (Table 1), the latter corresponding to

TABLE 1. *Deputy Regional Medical Heads of the Medical Division in Massachusetts, Conforming to the Eighteen District Medical Societies of the Massachusetts Medical Society*

BARNSTABLE Dr. John O. Niles Osterville	MIDDLESEX EAST Dr. Brainard F. Conley 51 Main Street, Malden
BEPKSHIRE Dr. Harry G. Mellen 150 North Street, Pittsfield	MIDDLESEX NORTH Dr. Marshall L. Alling 9 Central Street, Lowell
BRISTOL NORTH Dr. Lester E. Butler 148 High Street, Taunton	MIDDLESEX SOUTH Dr. Robert L. DeNormandie 330 Dartmouth Street, Boston
BRISTOL SOUTH Dr. Curtis C. Tripp 416 County Street, New Bedford	NORFOLK Dr. F. William Marlow, Jr. 1264 Beacon Street, Brookline
ESSEX NORTH Dr. Frank W. Snow 24 Essex Street, Newburyport	NORFOLK SOUTH Dr. Daniel B. Reardon 1186 Hancock Street, Quincy
ESSEX SOUTH Dr. Charles F. Twomey 88 Ocean Street, Lynn	PLYMOUTH Dr. Stanley E. Peterson The Checkerton, Brockton
FRANKLIN Dr. Halbert G. Stetson 39 Federal Street, Greenfield	SUFFOLK Dr. Charles F. Wilinsky Beth Israel Hospital, Boston
HAMPDEN Dr. William A. R. Chapin 121 Chestnut Street, Springfield	WORCESTER Dr. James C. McCann 390 Main Street, Worcester
HAMPSHIRE Dr. Edward J. Manwell 16 Center Street, Northampton	WORCESTER NORTH Dr. James G. Simmons 30 Myrtle Avenue, Fitchburg

the district societies of the Massachusetts Medical Society.

The functions of the director and his executive group are as follows: to simplify, standardize and integrate all the activities of the Medical Division; to send information and instructions to the regional medical heads and the chief medical officers or their deputies in each community; to assist and maintain a liaison with the other divisions of the Committee on Public Safety, with the Office of Civilian Defense and with the American Red Cross.

The function of the regional medical heads and the deputy regional medical heads is to assist in every way the work of the local medical organizations. They can be of assistance both in setting up the proper type of local medical committees and in helping them establish their organization and facilities. Furthermore, they are responsible for the designation of emergency and base hospitals in all communities of their respective regions. The regional heads and their deputies should go to the local communities and, by example and public addresses, should stimulate the people to organize and equip first-aid

†The names and addresses of the medical directors for the New England states are as follows: Maine—Dr. Allan Craig, Eastern Maine General Hospital, Bangor; New Hampshire—Dr. Charles H. Parsons, 33 Pleasant Street, Concord; Vermont—Dr. Charles F. Dalton, 2 Colchester Avenue, Burlington; Massachusetts—Dr. Elliott C. Cutler, Peter Bent Brigham Hospital, Boston; Rhode Island—Dr. Joseph C. O'Connell, 215 Thayer Street, Providence; and Connecticut—Dr. George M. Smith, Yale University School of Medicine, New Haven.

parties, medical first-aid posts, ambulance services, medical depots, and emergency and base hospitals.

In each region, the regional medical head is the rank-

tals and in many other ways. Furthermore, the regional medical heads and their deputies are responsible for lateral communications; that is, the chief medical officer of

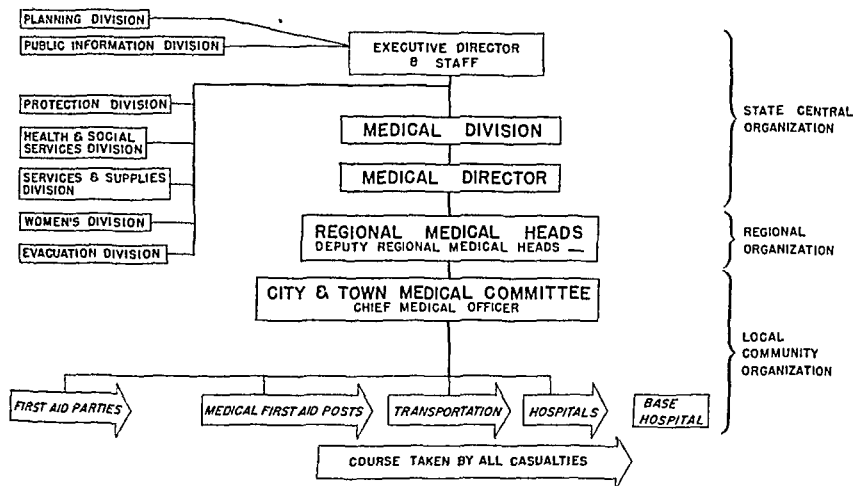


FIGURE 1. General Organization of the Medical Division

ing medical officer, and the deputy heads should assist him in every possible way. When a warning (yellow

each community suffering heavy damage should refer his request for additional personnel, supplies and equipment

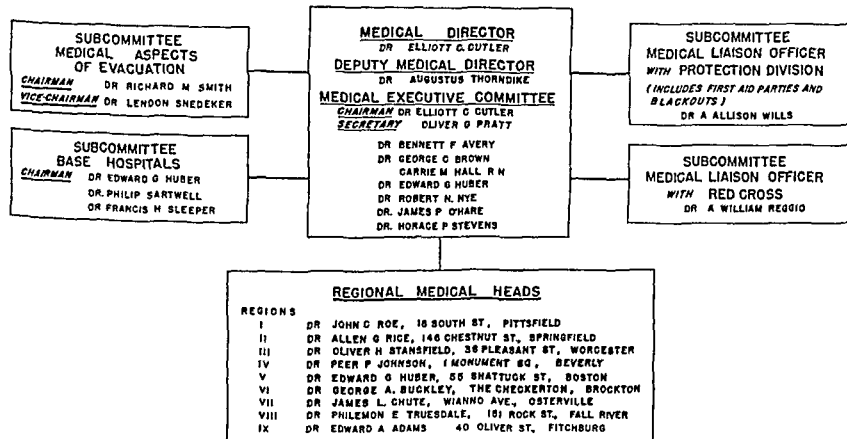


FIGURE 2. Personnel of the Central Organization of the Medical Division in Massachusetts

Since the drawing of this chart, Dr. Augustus Thorndike has resigned as deputy medical director and has been replaced by Dr. A. William Reggio, and Mr. Thomas P. Keating has been made a member of the Medical Executive Committee.

signal) comes, all should assemble at the regional headquarters; the deputy heads can be of great assistance in disseminating information to emergency and base hospi-

directly to the regional headquarters, rather than to an adjoining township. Finally, each regional head or deputy must provide an alternate to take his place, if necessary.

3. LOCAL MEDICAL ORGANIZATIONS. These vary according to the size and type of the community. There should be a medical committee in each community, with a physician as chairman, who may serve as the chief medical officer at the report center (so-called "control center" in the publications of the Office of Civilian Defense) or may appoint a deputy for this task. The chief medical officer should have complete authority over all medical services in the event of disaster and, as with every other post of the medical organization, should appoint a deputy.

On the medical committees in the large communities,

them to a *medical first-aid post* or *casualty station*. It is estimated that at least one such post is necessary for each unit of 10,000 inhabitants in any one report-center area. At the medical first-aid post will be physicians, nurses, male and female volunteers trained in first aid, and medical equipment. There, the necessary emergency medical procedures will be carried out. The patient will then be transferred, if necessary, to the designated *emergency hospital* and, later, if necessary, to a *base hospital*.

As previously mentioned, the scheme is flexible, and no set rules for organization can be established, since

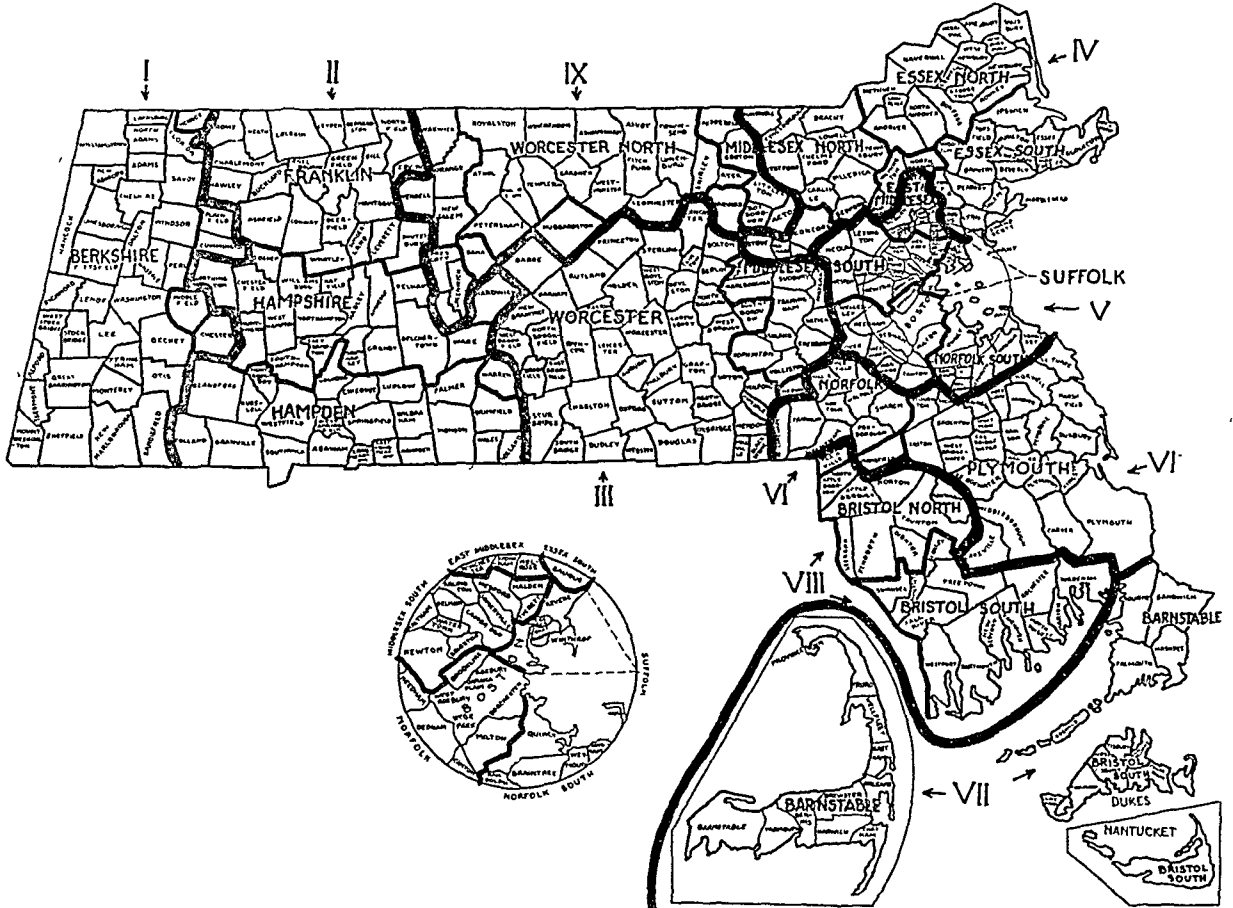


FIGURE 3. Map Showing the Boundaries of the Regions and of the District Medical Societies in Massachusetts.

there should be, in addition to the chairman, one individual representing the hospitals, one representing the local board of health, one dentist and one graduate nurse, as well as other representative physicians. It is further desirable that there be a Red Cross liaison officer, a pharmacist and representatives of all agencies within the community that might render medical assistance. Each community can best judge for itself how this group should be set up.

In small communities where there are few physicians and only occasional hospitals, two, three or even four adjoining towns should unite, centering their activities on a hospital common to all and arranging for ambulance transportation of casualties to this point.

4. GENERAL OUTLINE FOR CARE OF CASUALTIES. The care of civilian casualties begins at the site of disaster. Wardens of the ARP service who have been assigned to first-aid duty will act as *first-aid parties* (so-called "stretcher teams" in the publications of the Office of Civilian Defense), rescuing the injured and directing or transporting

what should be done in a rural community is obviously different from that in a metropolitan area.

5. LOCAL ORGANIZATION FOR CARE OF CASUALTIES. Report centers have been established throughout the State, ranging in number from one in small communities to many in large cities (Fig. 4 and Appendix A). If there is more than one report center in a community, the chief medical officer must appoint a deputy chief medical officer to serve as the ranking medical officer in each report-center area.

In the event of a warning (yellow signal) at the report center, the chief medical officer, the Red Cross liaison officer (if available), the chief air-raid warden and his deputy and the heads of the other services are notified and proceed immediately thereto; the members of the mobile medical services—first-aid parties, medical first-aid posts and ambulance service—are immediately ordered by the chief medical officer to the medical depot. At the same time, members of mobile canteens and other relief services are similarly mobilized at the medical depot (relief center). When a report center is notified of an

incident by the post warden, one or more medical service units, depending on the severity of the damage, proceed immediately, on notice from the chief medical officer, to the scene of disaster. They establish a medical first aid post in a satisfactory building as near the incident as possible, preferably within 200 yards.

The necessity for the chief medical officer to organize and train the personnel of the first aid parties and medical first-aid posts to perform as co-ordinated units not only among themselves but also with the ambulance and

One of the important duties of the chief medical officer is his relation to the American Red Cross and other relief agencies. Where practicable, there should be a Red Cross representative in each report center, who will assist the chief medical officer. In many report-center areas, the Red Cross will provide, under the direction of the chief medical officer, ambulance service and mobile canteens; it will also furnish food clothes and temporary shelter to uninjured citizens rendered destitute.

**a Mobile Medical Services** A mobile medical unit consists of two first aid parties and one medical first-aid post, comprising twenty-four persons, exclusive of the ambulance drivers. Transportation of the equipment and personnel of this unit will require at least four, preferably five automobiles—one passenger car and three, preferably four, ambulances. The chief medical officer is responsible for having these vehicles in readiness. In most report-center areas, the ambulances will be provided by the local Red Cross chapters, however, many commercial ambulance companies, undertakers and others have signified their willingness to supply the necessary vehicles. Fol-

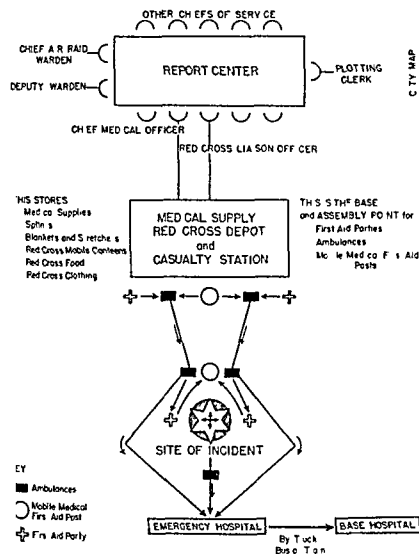


FIGURE 4 Community Organization at and from the Report Center

emergency hospital services, cannot be too strongly emphasized. Each community is responsible for this organization within its own limits, and the regional medical heads and their deputies should give assistance in creating efficient units. The care of casualties begins at the site where injury takes place. Smooth and rapid handling and co-ordinated treatment from the time the first-aid party removes the casualty is most important, since this reduces mortality and makes a favorable impression on the morale of the general public. Nothing but constant drilling and training can produce a smooth running organization. A spirit of comradeship and pride in efficiency will develop within the personnel when a sense of purpose and teamwork is attained.

In large metropolitan areas with deputies acting as chief medical officers in the various report centers, the chief medical officer should also appoint a deputy in charge of organizing all the hospitals in his district on a twenty-four hour basis. Also, in the event of severe and continued bombing, casualties should be evacuated from the emergency hospitals to base hospitals in the country. This is not the responsibility of the chief medical officer, he should report his needs to the regional medical head who will provide transportation and hospitalization through the evacuation officer.

IDENTIFICATION TAG			
Name	(Surname)	(Given name)	
Address			
Age			
Male	<input type="checkbox"/> Catholic	<input type="checkbox"/> Single	<input type="checkbox"/> White
Female	<input type="checkbox"/> Protestant	<input type="checkbox"/> Married	<input type="checkbox"/> Negro
	<input type="checkbox"/> Jewish	<input type="checkbox"/> Widowed	<input type="checkbox"/> Other
Person to be notified:			
Name			
Address			
Phone	Relation		
Where tagged			
Date	194	Hour	M
Diagnosis:			
Treatment given:			
Morphine		Tourniquet	
Where sent			
Signed			
Organization			

FIGURE 5 Identification Tag

lowing assembly at the medical depot and subsequent notice of disaster, the unit proceeds to the site of the incident.

**b First Aid Parties** A first aid party comprises six ARP wardens, assigned to first-aid duty, who operate under the commanding officer of the medical first-aid post. Each must have taken one of the first-aid courses

given by the American Red Cross and should be thoroughly trained as a stretcher bearer; he is equipped with a first-aid kit belt (Appendix B), and the party obtains stretchers and blankets from the medical first-aid post. The party should attach and fill out identification tags (Fig. 5), should give emergency medical care (first aid only) and should either transport the wounded by stretcher to the medical first-aid post or direct the walking to this post or to a casualty station (usually located at the medical depot). A casualty should *not* be taken, sent or directed to an emergency hospital unless it is so ordered by a physician from the medical first-aid post.

*c. Medical First-Aid Posts.* The personnel consists of two physicians, two graduate nurses, and four female and four male volunteers who have had Red Cross first-aid training and who can act as assistants and as stretcher bearers. One of the physicians should be made the commanding officer, with the responsibility of dispatching the first-aid parties to collect casualties, receiving and treating the wounded, and dispatching the ambulances to the emergency hospital.

The medical first-aid post requires at least two rooms, preferably with running water in each. The walking wounded should be directed to one of these rooms (or to the medical depot or other places equipped and staffed to function as casualty stations), and the stretcher cases should be taken to the other. Portable wooden or metal horses should be part of the equipment (kitchen tables, chairs and so forth can be improvised); on these, the stretcher should be placed, so that the patient can be splinted or given further medical treatment without being moved off the stretcher.

A chest (Fig. 6) containing the medical first-aid post supplies, and all other equipment (Appendix C), should be kept in a designated spot, preferably the medical depot, and

these tags are supplied to each medical first-aid post, as well as being in the kit belts of the first-aid parties. If the tag was not put on by the first-aid party, it must be attached and filled out at the first-aid post by the registrar; if only partly filled out, it must be completed. An additional official record must be kept by the registrar of each post, preferably in a *book*; and this must be turned in to the chief medical officer at the end of each tour of duty. The record should be brief but must include everything on the tag and a short account of the treatment, especially the administration of drugs, and of the disposition of the case.

Each medical first-aid post should have a duplicate or, preferably, triplicate personnel, so that service can be maintained on a twenty-four-hour basis, in twelve-hour or eight-hour shifts; even duplicate or triplicate sets of supplies and equipment may be provided.

*d. Medical Depots.* One or more medical depots are located in each report-center area. Fire stations, police stations and school buildings are suitable sites. There, the supplies and equipment of the first-aid parties, medical first-aid posts and casualty stations, for which the chief medical officer is responsible, are stored, and there, the personnel of these units and ambulances assemble in times of emergency. It will also be used by the Red Cross for the storage of its medical supplies. The officers in charge of medical depots need not be physicians—pharmacists or employees of medical-supply houses are quite suitable.

In densely populated areas, this depot may be used as a casualty station for the care of the lightly wounded, since it is desirable not to crowd the medical first-aid posts or the emergency hospitals with such minor cases. Furthermore, portions of the same building or adjacent buildings should serve as an assembly station for the Evacuation Division, and as a base for mobile canteens and a storehouse for the supplies and equipment required by the Red Cross for the clothing, feeding and housing of uninjured but destitute citizens.

Exchange of equipment between first-aid parties and medical first-aid posts will proceed as equipment is used. First-aid parties will go into a demolished area with their stretchers, blankets and first-aid kits. They will evacuate the wounded to the medical first-aid post, leaving the stretchers and blankets. There they will pick up reserve supplies of stretchers and blankets and, if necessary, gauze supplies for their emptied kit belts and will return to the scene of disaster to evacuate other casualties.

Auxiliary medical depots should be established in every emergency hospital for the interchange of stretchers, blankets and splints. When an ambulance evacuates stretcher cases with Keller-Blake or Murray-Jones splints from a medical first-aid post to an emergency hospital, the driver picks up at the hospital an equivalent number of stretchers, blankets and splints and returns to the medical first-aid post. The chief medical officer must see to it that such supplies are adequate at all times in all places and should replenish these supplies from the medical depot.

Although equipment must be exchanged, there should be *no* change in the assignments of medical, nursing and other personnel, other than relief after eight or twelve hours of continuous duty.

*e. Auxiliary Emergency Medical Depots.* The National Pharmaceutical Association and some of the state pharmaceutical associations, including Massachusetts, have offered to provide certain drugstores with supplies for the emergency use of physicians and first-aid-trained ARP wardens. It has been suggested that such stores be designated by

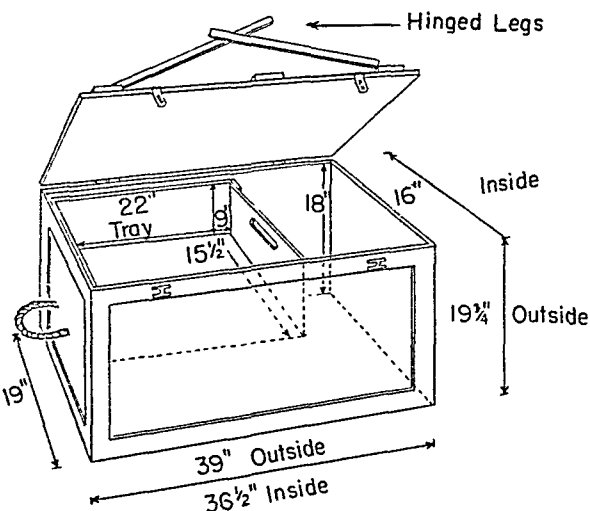


FIGURE 6. Box for Storage of Supplies, Instruments and Drugs of a Medical First-Aid Post.

should be transported by the ambulances when the mobile medical unit is ordered out. Each post should be equipped with at least three powerful electric lanterns operated by dry cells (for example, Red Bird lanterns), as well as with suitable material for blackout.

When the medical first-aid post is established, one member of this unit (preferably one of the female first-aid volunteers) should act as *registrar*. The wounded will enter with identification tags tied on by the first-aid party, on which certain data are to be written;

an appropriate window sign such as Emergency Medical Depot, they will have a cabinet where compress bandages, triangle bandages and supplementary wooden splints are stored.

*f Casualty Stations* In metropolitan areas, the chief medical officer may deem it advisable to establish casualty stations for the treatment of the less seriously wounded. These may be located at the medical depots, as previously mentioned, or at other strategic sites, emergency hospitals should *never* be used for this purpose. As at the medical first aid posts, a record of all casualties must be kept and turned in daily to the chief medical officer.

*g Transportation* Transportation of the personnel and equipment of the first aid parties and medical first aid post to the scene of disaster is provided by passenger cars and ambulances, and that of the seriously wounded from the first aid post to the emergency hospital by ambulances. When ordered by the chief medical officer, the drivers report to the medical depot with their cars. If a sufficient number of ambulances are not available through the Red Cross or otherwise, the chief medical officer must provide for additional vehicles, with drivers. So far as possible, police-department and fire department ambulances should not be used, since they will probably be needed for other emergency purposes. The commanding officer of the medical first aid post is responsible for the evacuation of patients to the emergency hospital. The ambulances should be operated by the shuttle system, whenever possible.

Beach wagons and one ton or one and a half ton panel body delivery trucks may be converted for ambulance use. In fact, any kind of delivery vehicle or small truck on the floor of which can be placed two stretchers will serve the purpose.

Two drivers should be detailed to each ambulance, and both should be trained in first aid care. Members of the Red Cross Motor Corps and women trained by the Women's Civilian Defense School have had such training in addition to experience in convoy duty and driving under black-out conditions.

*h Emergency Hospitals* In each community, the medical committee should organize the existing hospitals for casualty service. This means that the staff physicians, dentists and nurses should be allocated to two twelve hour or three eight hour shifts. Small communities should be so organized, as previously mentioned, that the nearest hospital is available. All hospitals used as emergency hospitals should increase their supplies of medical material and of permanent food, such as canned goods. Such hospitals should also carefully study the black-out regulations outlined in two manuals, *Blackout Information to the General Public* and *Blackout Information, Lighting and Ventilation for Industrial Plants and Commercial and Public Buildings*, compiled by the Protection Division of the Massachusetts Committee on Public Safety, and in a booklet, *Protective Construction Series No. 1 Glass and glass substitutes*, issued by the Office of Civilian Defense, Washington, D. C., and equip themselves for such an event. In the large centers, the hospitals should begin the training of nurses aides, preferably under the new Red Cross system, in which a satisfactory preliminary training can be given to volunteers from the lay public. Once such training has been completed, the volunteer nurses aides should keep in practice by periods of active duty in the hospital every three or four months or by continuous service.

An experienced surgeon should be in charge of the disposition of all casualties brought to the hospital by ambulance.

All emergency hospitals should be equipped with the necessary furnishings for two, preferably three operating rooms for seriously injured cases, with operating teams, anesthesia service and nursing personnel so that at least two, preferably three operations may be carried on at the same time. If an air raid occurs in any sizable community, the emergency hospital is expected to double or triple the personnel so that the operating rooms may be used on continuous twenty four hour service (either twelve hour or eight hour shifts). This service is essential but will vary somewhat with the size and population of the community. In urban areas, it is essential that the hospital have protected operating rooms with independent lighting systems, preferably in the basement, where they will be protected from bomb splinters and broken glass and where they may function undisturbed.

In urban areas all casualties should be prepared for evacuation to a base hospital the next day, if the circumstances warrant.

The emergency hospitals, as previously stated, must have available at the ambulance entrance an adequate supply of stretchers, blankets and splints, to interchange supplies with incoming ambulances. Such supplies should be obtained from the medical depot.

In large and moderately sized hospitals, outpatient department facilities must be made available, on a twenty four hour basis for the less seriously injured ambulatory casualties (walking wounded) who have not been to a medical first aid post. The flow of patients should be arranged on a one way traffic basis so that large numbers can be handled without confusion, and an experienced surgeon should be in charge since many apparently minor injuries may be extensive and severe. Those with minor injuries should be evacuated to their homes, whenever possible, but should receive clinic treatment daily until ready for discharge to full employment or civilian life. In the metropolitan areas special dressing stations may be set up or the casualty stations used for the care of those who are ambulatory.

*Members of permanent hospital staffs should not be used as personnel in medical first aid posts, because in an emergency they will be more necessary at their hospitals.*

All emergency hospitals, on orders from the chief medical officer, should discharge to their homes, to previously designated convalescent homes or to base hospitals as many of their regular patients as possible—this should mean about 50 per cent of the census. Furthermore the emergency hospitals should acquire sufficient cots, blankets, splints, drugs and other medical supplies to provide for 25 per cent more than the average census.

**6 BASE HOSPITALS** As soon as possible after adequate surgical care has been completed, all casualties in emergency hospitals should be evacuated to large hospitals in the country, chiefly sanatoriums and hospitals under state control. This evacuation of patients will be accomplished by truck, bus or train and will be supervised by the regional medical head or a deputy appointed by him.

**7 MEDICAL ASPECTS OF EVACUATION** In any disaster only a portion of the population in the area will be injured, but many others will be rendered homeless and frightened. The latter may need clothing, temporary shelter and an opportunity to reunite their families or to plan for the future, furthermore, serious medical conditions may arise. The medical care of the noninjured civilian population is the responsibility of the Evacuation Division, which has its own medical organization, distinct from the Medical Division but working in close co-

operation with it. At regional and local levels similar liaison should obtain between these two medical groups. Food, clothing and temporary shelter for these refugees will be provided by the American Red Cross.

Evacuation of the civilian population involves more than emergency service at the time of disaster. People living in areas near military reservations or on islands may have to be moved to less dangerous regions; other areas may be within the theater of military operations. In any large-scale preplanned evacuation, preference would have to be given to mothers and children, the aged, the infirm and the handicapped. Such groups would necessarily create special medical problems in areas to which they might be evacuated. Educational, recreational and social-service facilities would have to be provided, together with the appropriate personnel, by arrangement with the Division of Health and Social Service. The organization to meet the various situations and the medical responsibilities entailed are described in bulletins and manuals prepared by the Evacuation Division. Reception areas will be established to which evacuees will be sent. At these points, medical care of the evacuees will be provided by the Evacuation Division until the emergency is over.

8. DECONTAMINATION. The control and care of gassed individuals who are not wounded will be handled by a special unit of the Protection Division. Men who have been instructed in marking out contaminated areas and in the care of burned and gas-contaminated patients will be detailed for this work. Those who wish to study the methods of decontamination in detail should consult the special pamphlet on gas defense that has been issued by the Protection Division.

From the point of view of the Medical Division, it must be clearly understood that nonwounded gassed patients should *not* be routed to emergency hospitals. The commanding officer of the medical first-aid post should send all gas casualties, after whatever emergency surgical care is necessary, to a decontamination center. This will avoid overcrowding the hospitals with people who usually need only a bath and change of clothing, and will prevent further contamination of valuable personnel with gas; furthermore, the hospitals could not possibly handle this type of casualty without considerable addition to personnel and equipment.

9. CARE OF THE DEAD. Proper disposition of the dead is important from the point of view of morale of the general public and of the mobile medical units and emergency hospitals. Arrangements should be made with the local medical examiner for the immediate removal of the dead. The ARP wardens should segregate the dead from the injured, and should send the former, not to a medical first-aid post or to a hospital, but to a center previously designated by the medical examiner, transportation being accomplished by ambulance. So far as possible, the dead should be kept from view. It is a surprisingly favorable commentary on the system in London that few people there have seen many dead casualties, in spite of heavy loss of life.

\* \* \*

#### APPENDIX A. *Data Concerning Report Centers, Medical First-Aid Posts, First-Aid Parties, Ambulances and Medical Depots in a Large City.*

The following is the proposed setup in Boston, with a population of about 840,000.

*Report Centers.* Twelve report centers will be established.

*Medical First-Aid Posts.* On the basis of 1 medical first aid post for each 10,000 inhabitants, there should be approximately 84 posts, or 7 posts attached to each report center.

*First-Aid Parties.* On the basis of 2 first-aid parties for each medical first-aid post, there should be approximately 168 parties, or 14 parties attached to each report center.

*Ambulances.* On the basis of 3 (preferably, 4) ambulances for each mobile medical unit (1 medical first-aid post and 2 first-aid parties), there should be approximately 252 (preferably, 336) ambulances, or 21 (preferably, 28) ambulances serving each report center. (As a matter of fact, this large number of ambulances is unnecessary in such a densely populated region, since it is extremely unlikely that all areas would be hit at any one time and since the exchange of ambulances from one report center to another is easily accomplished.)

*Medical Depots.* Since each report center should have at least 1 medical depot, there will be a minimum of 12 medical depots. The medical depot or depots in each report center might be called on to supply 7 medical first aid posts, 14 first-aid parties and 21 (preferably, 28) ambulances.

#### APPENDIX B. *Contents of Kit Belt for First-Aid Party.*

A first-aid kit belt contains the following:

- 1 pkg. Bandage compresses, 2 in., 4 per pkg.
- 1 pkg. Bandage compresses, 3 in., 2 per pkg.
- 2 pkg. Bandage compresses, 4 in., 1 per pkg.
- 1 yd. Gauze, absorbent
- 1 Bandage, gauze, 4 in.
- 2 Bandages, cravat triangle, nonsterile
- 1 pkg. Adhesive compresses, 1 in., 16 per pkg.
- 2 pkg. Tannic acid jelly
- 1 pr. Scissors
- 1 pr. Tweezers
- 1 Lipstick, red (for marking tourniquet cases)
- 1 Pencil, indelible (for identification tags)
- 10 Tags, identification.

The first six items will be supplied by the American Red Cross; applications should be made to the First Corp Area Emergency Office, 161 Massachusetts Avenue, Boston.

#### APPENDIX C. *Supplies, Instruments, Drugs and Equipment of a Medical First-Aid Post.*

The supplies, instruments, drugs and equipment of a medical first-aid post are as follows:

##### SUPPLIES

- 6 pkg. Red Cross "units," 2 gauze kits and 2 table covers per pkg.
- 2 pkg. Towels, 12 per pkg.
- 2 pkg. Bandages, gauze, 2 in., 12 per pkg.
- 2 pkg. Bandages, gauze, 3 in., 12 per pkg.
- 2 pkg. Slings, 6 per pkg.
- 1 pkg. Binders, scultetus, 4 per pkg.
- 1 roll Tape, adhesive, 1 in., 10 yd.
- 1 roll Tape, adhesive, 2 in., 10 yd.
- 1 box Throat sticks, wood, 10 per box
- 2 Mouth gags, wood
- 12 ft. Rubber tubing (for tourniquets)
- 5 rolls Cotton, absorbent, 1 lb. each
- 1 box Pins, safety
- 24 rolls Sheet wadding, 24 in.
- 4 pr. Gloves, rubber, Sizes 7½ and 8

- 4 Catheters, urethral, No 14 Fr
- 50 Cups, waxed paper
- 12 Splints, brasswood, 30 x 3½ x 3/16 in
- 4 Brushes, nail
- 6 cakes Soap
- 2 boxes Matches
- 1 Lipstick, red
- 1 Pencil, indelible
- 200 Tags identification

## INSTRUMENTS

- 2 Scissors Mayo, curved, 6 in
- 2 Knife handles, Bard-Parker No 3
- 12 Blades, Bard-Parker No 10
- 6 Snaps, straight 5½ in
- 6 Snaps curved, 6¼ in
- 4 pr Forceps, toothed, 6 in
- 2 pr Forceps, smooth, 6 in
- 12 Needles, Keith
- 12 Needles, full curved, Ferguson or Mayo 3½ in curve
- 50 tubes Ties, black silk, sterile (No 4 Gudebord)
- 6 tubes Sutures, catgut, sterile, No 1 plain
- 12 tubes Sutures, catgut, sterile, No 1 chromic
- 2 Shears, bandage, 7½ in
- 2 Syringes, Luer, 2 cc
- 12 Needles, hypodermic, 25 gauge
- 6 Flashlights, pencil type
- 1 Blood pressure apparatus
- 1 Stethoscope
- 1 Airway tube, Connell, large (3¼ x 7/8 x 3 9/16 in)
- 1 Airway tube, Connell, small (2¼ x 3/4 x 3/8 in)
- 2 Retractors
- 1 Tube tracheotomy
- 1 Razor, safety, with 20 blades
- 1 Razor straight
- 1 Stove (No 520, Coleman)
- 3 Lanterns, electric, dry-cell type (Red Bird)
- 2 Batteries, extra (for lanterns)

## DRUGS

- 50 pkg Sulfanilamide, powder, sterilized 4 gm each
  - 50 pkg Sulfathiazole, powder, sterilized 4 gm each
  - 1 qt Alcohol 70 per cent
  - 2 bot Morphine sulfate, sterile solution 20 cc each with rubber-diaphragm stopper (1 cc contains ¼ gr morphine sulfate)
  - 12 amp Nikethamide, 15 cc each
  - 2 pkg Chlorinated lime mixture, dry, in airtight tin, each containing
    - Chlorinated lime (30 per cent chlorine) 200 gm
    - Sodium bicarbonate 200 gm
    - Sodium carbonate, CP, anhydrous 80 gm
- For use, mix a portion of the dry powder in the hands with sufficient water to form a thin cream 4 minutes' rubbing with this cream is equivalent to 20 minutes' scrubbing
- 1 bot Aromatic spirits of ammonia, 2 oz
  - 6 pkg Tannic acid jelly, 2 oz each
  - 6 tubes Vaseline, white, 2 oz each
  - 1 qt Givoline in nonleaded can (for stove)

## EQUIPMENT

- 4 Trays solution, 3 in deep, nested
- 1 Sterilizer, enamel, with cover (to nest with trays)
- 2 Pails galvanized 10 qt
- 2 Sheets rubber 7½ x 25 in

- 2 Aprons, rubberized
- Blackout fabric
- 2 Tables, folding 30 x 30 in
- 2 Horses, wood or metal
- 6 Stretchers
- 12 Blankets
- 6 Splints, leg Keller-Blake
- 6 Splints, arm, Murray-Jones
- 1 Medical first aid post marker

All supplies, instruments and drugs are best packed in a wooden chest with rope handles (Fig 6), although bags of waterproof material or fiber suitcases will suffice.

The first six items of equipment can be packed in a duffle bag, and the remaining items should be placed in the ambulances in the most convenient places.

## BOOK REVIEWS

*Clinical Practice in Infectious Diseases for Students, Practitioners and Medical Officers* By E H R Harnes, MD (Lond), MRCP, DPH With a foreword by W Allen Daley, MD (Lond), FRCP, DPH 8°, cloth, 468 pp, with 31 illustrations and 28 tables Baltimore Williams and Wilkins Company, 1940 \$6.00

This is an up to date, trustworthy manual of the acute infectious diseases. After preliminary considerations of infection and resistance, transmission, serum sickness, general diagnosis and management, and the like, the individual maladies are considered in the usual fashion—definition, cause, clinical picture, pathology, complications, treatment, prevention, if any, and general management from the point of view of public health. The public health laws to which reference is made are, of course, British and not American.

This book will be most useful perhaps to the student brushing up or to the general practitioner venturing so little into these fields that he finds himself growing a bit rusty.

*A Primer for Diabetic Patients. An outline of treatment for diabetes with diet, insulin and protamine zinc insulin including directions and charts for the use of physicians in planning diet prescriptions.* Seventh edition, reset. By Russell M Wilder, MD 12°, cloth, 184 pp, with 11 tables 7 illustrations and 1 plate Philadelphia W B Saunders Company, 1941 \$1.75

The seventh edition of this excellent manual emphasizes the combination of protamine zinc insulin and regular (or crystalline) insulin in one injection. Definite rules for the adjustment of insulin doses are given, which provide for reduction of dose as improvement occurs. While insulin is being used Wilder encourages the patient to permit traces of sugar in the urine at all times, to avoid reactions. Average diets contain not more than 167 gm carbohydrate. Low fat and undernutrition diets are avoided. Directions for the management of coma, hypoglycemia and other complications are included. Both physician and patient will find the book most useful.

*Hydrotherapy in Psychiatric Hospitals* By Rebekah Wright, MD 8°, cloth, 334 pp, with 91 illustrations Boston The Tudor Press, 1940 \$4.00

This book is a revision of *Hydrotherapy in Hospitals for Mental Diseases*, published in 1932 by the same author. Dr Wright has rearranged the text, added descriptions of a few new procedures and inserted more illustrations.



The first part of the book is meant for physicians who prescribe hydrotherapy in psychiatric hospitals. The second part, directed to nurses and hydrotherapists, presents detailed descriptions of technics utilized in applying cold packs, continuous baths, irrigations and other forms of hydrotherapy so frequently made use of in mental hospitals.

The author is director of hydrotherapy for the Massachusetts Department of Mental Health, and physicians working in psychiatric hospitals in Massachusetts have been familiar with her work for a long time. The technics that she describes are standard procedures in the state hospitals.

Physicians interested in utilizing hydrotherapy in the treatment of their patients will be glad to see this revision of Dr. Wright's book.

*Modern Dermatology and Syphilology.* By S. William Becker, M.D., and Maximilian E. Obermayer, M.D. 4°, cloth, 871 pp., 461 illustrations and 32 colored plates. Philadelphia: J. B. Lippincott Company, 1940. \$12.00.

Several unusual and acceptable features appear in this book. In the first place, the functional aspects of skin disease are emphasized. Secondly, it is less encyclopediac than most of the textbooks on dermatology, unusual diseases and tropical diseases being hardly mentioned. On the other hand, more space has been allotted to the commoner and more important dermatoses. The term "eczema" is not used, but there is a thorough discussion of the effects of external agents on the skin under the headings of "Toxic Dermatoses," and of the effects of internal factors and of certain functional diseases of the skin under the title "Neurodermatoses." In the latter group are included the following: idiopathic pruritus of various types, neurotic excoriations, neurodermatitis, dyshidrosis, chronic urticaria and alopecia areata. The authors have made a real contribution to dermatology by their investigations of this group and in frequently indicating their relation to other functional diseases, such as colitis, rhinitis and migraine. In fact, the general relations of skin disease to the bodily economy are emphasized throughout the book, in accordance with the authors' statement, "Its diseases are reflected in changes in other parts of the organism and it often mirrors internal diseases."

The chapter on pigmentary diseases is another outstanding contribution. Becker has done much investigative work with pigment, and the classification of pigmentations at the beginning of the chapter and the discussion of these diseases present the opinion of an authority on the subject.

Each chapter contains a paragraph of explanation that discusses the relation of the subject of the chapter to other subjects or brings out points of general interest concerning the subject under consideration.

Therapy is discussed in the introductory chapter, with a formulary and explanations of individual therapeutic procedures. In the discussion of the therapy of an individual dermatosis, the lists of procedures detailed by previous authors are often less complete than those in the usual textbooks. However, the authors discuss treatment from their experience with patients at the University of Chicago clinics. In the management of the functional dermatoses, their method is given in considerable detail; this has been of decidedly practical value, and should be helpful to the average physician in the handling of such cases. The discussion of syphilis is especially full and reviews the general manifestations of the late type and their therapy in more detail than the average dermatologic text.

Excellent photographs supplement the text, and of particular value are the color plates, which are indispen-

sable in the presentation of skin manifestations. Of value also are the tables on cutaneous lesions, lists of etiologically important plants, weeds and trees, and lists of patch-test dilutions and drugs.

Taken altogether, the title is well chosen, and a modern viewpoint of dermatology is well presented, particularly in the four introductory chapters on the neurodermatoses, the pigmentary diseases, therapeutic methods and syphilis.

*Electrocardiography, Including an Atlas of Electrocardiograms.* By Louis N. Katz, M.D. 4°, cloth, 580 pp., with 420 engravings, including 806 electrocardiograms. Philadelphia: Lea and Febiger, 1941. \$10.00.

*Exercises in Electrocardiographic Interpretation.* By Louis N. Katz, M.D. 4°, cloth, 222 pp., with 128 engravings containing 189 electrocardiograms. Philadelphia: Lea and Febiger, 1941. \$5.00.

These two volumes supplement each other, the latter furnishing illustrations for practice in applying the principles of the former. The textbook itself, however, is lavishly illustrated, and it amply confirms the claim that it contains "an atlas of electrocardiograms." The combination of these books really constitutes a complete course of clinical electrocardiography and justifies their high cost.

The plan of the larger volume consists of a division into three main sections, with sixteen chapters and a separate bibliography for each section. The sections are, "Theory of Electrocardiography," "Systematic Description of the Electrocardiographic Contour" and "Systematic Description of the Electrocardiogram in the Arrhythmias."

The first section gives an excellent background in the bioelectric phenomena involved in electrocardiography. Because of his own investigations, the author has deserted to a considerable degree the principle of vector analysis of these phenomena. This remains disputed ground but alters little the clinical aspects of the subject. Anatomy and physiology are adequately considered, and the illustrations are excellent. The place of the electrocardiogram in clinical practice is defined, and one sentence might be framed in the conscience of each practitioner of this art "In short, the electrocardiograph is not a tool for the unscrupulous, or a plaything for the erudite, nor is it an instrument of precision which replaces the ordinary clinical examination."

The second and third sections may also be approved without important reservations. The precepts are sound, and the examples carefully selected. Clinical relations, electrocardiographic findings in various diseases and the influence of digitalis are emphasized, as is the therapy of the various arrhythmias. A preponderant space is properly given to coronary heart disease.

The so-called "exercises" consist of 90 unknown cases with electrocardiograms from which interpretations are made and correlated with the clinical data. When helpful in the analysis, serial tracings on the same patient are shown. In each case, the electrocardiogram is illustrated and studied under the following headings: description, interpretation, clinical story and correlation. Preceding the unknown cases is a short section on the technique of the approach to an electrocardiogram, and the steps necessary in its analysis. For this reason alone, the volume is useful to one with some knowledge of the subject, particularly for a review of his own interpretations in the light of the most recent cardiovascular knowledge.

The reviewer recommends the work wholeheartedly. It demonstrates, beyond question, not only that electrocardiography is of great practical importance, but also that it is a lively and developing science.

(Notices on page x)

# The New England Journal of Medicine

Copyright 1942 by the Massachusetts Medical Society

VOLUME 226

JANUARY 15, 1942

NUMBER 3

## RESULTS OF FIFTEEN YEARS OF THE CANCER-CONTROL PROGRAM IN MASSACHUSETTS\*

HERBERT L. LOMBARD, M.D.,<sup>1</sup> AND FRANCES A. MACDONALD, A.B.<sup>†</sup>

BOSTON

FIFTEEN years ago, the Commonwealth of Massachusetts inaugurated a cancer control program with three objectives: the prevention of cancer, the early recognition and treatment of the disease, and the increase of existing knowledge by the scientific analysis of every fact and record available. To attain these objectives, diagnostic cancer clinics, treatment centers, research and education were necessary. The care and treatment of the incurable case might have been considered for humanitarian reasons, but this activity did not come logically under the heading of cancer control. The Massachusetts Cancer Program from its inception has comprised five parts: statistical research, tumor diagnosis service, hospitalization, diagnostic clinics and education. The evolution of the program has been presented in the literature. An appraisal of the results of cancer control in Massachusetts, together with indications of future trends, is given in this report.

The evaluation of a program of cancer control differs markedly from that of one directed against a communicable disease. Within a few days in the presence of a smallpox epidemic, the results of vaccination are apparent. Even with rabies, the time element is short compared with that of cancer, in which years may elapse between the beginnings of a chronic irritation and a subsequent cancer. Neither measures directed at the prevention of cancer through the elimination of chronic irritations nor those attempting effective therapy may be evaluated until after an interval of years.

The best criterion of measurement is the adjusted death rate. Other criteria are the various delays before therapy, the increased interest of the medical profession and the laity, and the attend-

ance at clinic and hospital. The period in which the Massachusetts Cancer Program has been functioning has been long enough to warrant appraisals by all these methods.

In the state aided clinics, the delay between the first recognized symptoms of the disease and the time the patient presents himself to a physician is one measure of the effectiveness of education of the laity. In the early years of the cancer program, this delay averaged 65 months. Between 1936 and 1939, it was 53 months, and in 1940, 46 months. A similar estimate of the effectiveness of education is the percentage of patients with cancer who go to their physicians within the first month of recognized symptoms. In 1940, 21 per cent of the clinic cancer patients went to their physicians within the first month of their symptoms, as compared with 15 per cent in the early years of the program. A second period of delay is that between consulting the first physician and visiting the cancer clinic. This delay, which may be attributed to either physician or patient, or both, has been decreasing rapidly and is now about half what it was in the early years of the clinics. The third delay is between presentation at the clinic and the institution of treatment. The social workers in the clinics have helped to reduce this delay. About two thirds of the patients are treated within one week, and over 90 per cent within one month of first clinic visit. There has also been considerable curtailment in this period of delay since the early years of the clinic.

The sum total of these delays, however, amounts to more than one month in the majority of cancer cases in the clinics. Only a small percentage of patients receive therapy within one month of the first symptoms. In the early years of the clinics, the percentage being treated in one month was 31; in 1939, it had increased to 58. The shortening of all these intervals of delay points toward

\*Read before the annual meeting of the clinic chiefs of the State Aided Cancer Clinics Boston May 29, 1941.

<sup>1</sup>Director Division of Adult Hygiene Massachusetts Department of Public Health (Paul J. Jakmuth, Commissioner).

<sup>†</sup>American Division of Adult Hygiene Massachusetts Department of Public Health.

improvement in the cancer situation in Massachusetts (Table 1).

Although the adjusted cancer death rate is used for most comparisons, the actual number of deaths is of importance from an administrative standpoint,

TABLE 1. *Annual Percentage Change.*

Annual percentage reduction in delay of cancer patients before going to first physician	39
Annual percentage reduction in delay of cancer patients before attending clinic	44
Annual percentage reduction in delay of cancer patients between clinic and treatment	38
Annual percentage increase of number of physicians referring patients to clinic	105
Annual percentage increase in cancer deaths	23
Annual percentage increase of specimens sent to Tumor Diagnosis Service	45
Annual percentage increase of clinic admissions of cancer patients	110
Annual percentage increase of general-hospital admissions of cancer patients	47

since measures directed toward care and treatment depend on numbers rather than rates. During the period of the Massachusetts Cancer Program, the actual number of deaths has increased annually by about 2 per cent. During this same period, the clinic attendance of cancer patients has increased annually about 11 per cent, the number of specimens sent to the diagnostic laboratories about 4.5 per cent, and the admissions to general hospitals about 5 per cent. This latter figure is of particular significance inasmuch as additional facilities for cancer patients at the Pondville, Westfield and Palmer Memorial hospitals have been made available during the period.

Additional evidence is obtained from samples from the death records of 1932 and 1940. In 1932, 31.1 per cent of the fatal cases had never been treated in a cancer hospital for the disease. In 1940, this figure had been reduced to 15.8 per cent. Hospitalization for cancer is increasing far more rapidly than the cases of the disease.

Although the attendance of new cancer patients at the state-aided clinics has increased five times as fast as the deaths, only about 8 per cent of the cancer population are seen in the clinics. The other 92 per cent make use of other facilities for diagnosis.

The effect of the clinics, however, is of far greater consequence than the actual number of cases seen. Each clinic acts as a center of cancer interest for the surrounding territory, and the consciousness of cancer of both the public and the profession is enhanced. Moreover, teaching clinics furnish postgraduate instruction for the medical profession. Between sixty and seventy of these clinics are held each year, and over 1300 physicians attend them. Although the cancer

clinics admit about 1800 new cancer patients each year, the total attendance comprising new and old cancer patients and persons who are found to be free of malignant lesions numbers approximately 21,000.

Since the opening of the cancer clinics, approximately 14,000 patients with cancer have attended the clinics. Forty per cent of these are still alive. At the end of ten years after coming to the clinic, 47.0 per cent of the patients with cancer of the skin were alive, 23.3 per cent with cancer of the mouth, 21.6 per cent with cancer of the uterus, and 15.6 per cent with cancer of the breast. Inasmuch as ten years after clinic admission the dying-off curve for the clinic patients is almost identical with that of the Massachusetts population, most of these cases may be considered to be cured.

The changing attitude of the public and the profession toward the cancer program may not be considered an actual measurement of accomplishment, but it does seem to be an indication of existing trends. During the period of the program, questionnaires have been sent to the physicians of the State several times requesting frank comments on the program. In the first few years, there were a large number of adverse comments coupled with constructive criticism. The latest questionnaire, answered by about 1500 physicians, revealed only one adverse comment. Some of the physicians who did not answer were doubtless not in sympathy with the program, but a change so great as this indicates the change in professional opinion. The physicians are also giving their time to address meetings of the co-operative cancer-control committees. In Boston, it was found that two thirds of the doctors were willing to speak, whereas in the smaller communities the percentage is often 100. Steadily increasing numbers of physicians are referring patients to the cancer clinics. In 1940, physicians referred 80.8 per cent of the patients to the clinics. This is in sharp contrast with the 20.1 per cent who were referred in the first year of the program. The number of physicians making use of the tumor diagnosis service has increased. Between 1927 and 1935, there were 421 physicians who used this service, and in 1940 there were 798. In the same period, the number of specimens increased from 2813 to 3907. The increase in the number of doctors using this service has been greater than the increase in the number of specimens. Monthly bulletins, containing excerpts from the cancer literature, and the volume *Cancer: A manual for practitioners*, which have been furnished by the department to physicians in the State, have been

well received, as evidenced by the large number of letters received from the profession.

The public has shown a remarkable change in attitude. In the early days of the program, it was rather difficult to obtain an audience of any size if cancer was the subject under discussion. Meetings were arranged, with talks scheduled on chronic disease and adult hygiene, simply to cover the subject of cancer. Today, the members of the co-operative cancer control committees number over 10,000 and usually have little difficulty in arranging for cancer meetings.

Real comparisons of the prevalence of disease between communities and between different intervals in the same community cannot be revealed by crude death rates, if the age-sex composition of the

bly indicates improvement in diagnosis of the primary site of cancer, and that cases formerly called stomach and liver are now being assigned to other locations.

Inasmuch as a decided drop in the cancer rate among females began in 1935 in Massachusetts, additional computations were made of the adjusted rates of Massachusetts from 1900 to 1939, compared with the eleven states that comprised the Registration Area of 1900. Between 1900 and 1925, the trend for males was upward in both Massachusetts and the Registration Area, and the annual percentage increase was only slightly higher in the latter than in the former. Among females during the same period, the rates for Massachusetts and the Registration Area were both up-

TABLE 2. *Average Annual Percentage Change in Rate of Mortality from Cancer (1920-1935) by Geographic Sections of United States.\**

SECTION	TOTAL CANCER	BUCCAL CAVITY	STOMACH AND LIVER	PERITONEUM INTESTINES AND RECTUM	SKIN	BREAST	FEMALE GENITALS	OTHERS
	%	%	%	%	%	%	%	%
Registration area, 1920 (38 states)	+1.01	-0.50	-1.04	+2.10	-1.75	+1.82†	+0.85†	+3.71
Northeast‡	+1.17	-0.48	-0.72	+1.98	-1.90	+1.42†	+0.55†	+3.53
Massachusetts	+0.50	-0.52	-1.00	+1.26	-1.93	+0.68	+0.09	+2.75

\*All trends based on age adjusted rates

†Percentage computed by Gover.<sup>1,2,3</sup>

‡Connecticut, Delaware, District of Columbia, Maine, Maryland, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island and Vermont

states varies and the disease has a predilection for certain age groups. A common base of comparison mathematically figured, by adjusting the age distributions by states to a standard population, makes possible a more accurate appraisal. Gover's<sup>1-3</sup> comprehensive study of cancer mortality in the United States shows that great differences in adjusted rates occur between the different sections of the country, and the trends of these rates also differ. With Gover's method of comparison and some of her calculations, Table 2 was constructed. This shows the comparison between Massachusetts, the Registration Area of 1920, which included thirty-eight states, and northeast United States, which includes Massachusetts and eleven other states. The average annual percentage change in the rate of mortality from total cancer, from cancer of the peritoneum, intestines and rectum, from cancer of the breast, from cancer of the female genitals and from cancer of other organs was much less in Massachusetts. There was not much difference between Massachusetts and the Registration Area in cancer of the buccal cavity, in cancer of the skin, and in cancer of the stomach and liver. The decrease shown in cancer of the stomach and liver proba-

ward, but to a lesser degree than among males, and both annual percentage increases were almost identical. In the period of the Massachusetts Cancer Program, 1926-1939, the males in Massachu-

TABLE 3. *Annual Percentage Change in Adjusted Cancer Death Rates in Massachusetts before and during Cancer Program, Compared with Similar Periods for the Registration States of 1900.*

PERIOD	MASSACHUSETTS %	REGISTRATION STATES OF 1900*
Before program (1900-1925)		
Males	+2.37	+2.49
Females	+1.38	+1.31
During program (1926-1939)		
Males	+1.16	+2.19
Females	-0.21	+0.71

\*Connecticut, District of Columbia, Indiana, Maine, Massachusetts, Michigan, New Hampshire, New Jersey, New York, Rhode Island and Vermont.

setts had a much lower annual percentage increase than the males in the Registration Area, whereas the females in Massachusetts had a 0.2 per cent drop, contrasted with an 0.7 per cent rise in the Registration Area (Table 3).

\* \* \*

This summarizes the accomplishments in cancer control in Massachusetts during the last fifteen

years. One cannot postulate that all the improvement has been due to the Massachusetts Cancer Program. The American Society for the Control of Cancer has worked for over a quarter of a century. The American College of Surgeons has been extremely active, and in the last few years the federal government has inaugurated an extensive cancer program. There may even be forces at work of a biologic nature of which we have no knowledge. However, it seems reasonable to assume that a part of this improvement is due to the constructive efforts of over 7000 physicians in Massachusetts, of the hospitals of this state, of the members of the co-operative cancer-control committees and of the Massachusetts Department of Public Health, which together constitute the Massachusetts Cancer Program.

## REFERENCES

1. Gover, M. *Cancer Mortality in the United States: Trend of recorded cancer mortality in the death registration states of 1900 from 1900 to 1935*. U. S. Public Health Service, Public Health Bulletin No. 248. 58 pp. Washington: Government Printing Office, 1939.
2. *Idem*. *Cancer Mortality in the United States: II. Recorded cancer mortality in geographic sections of the death registration states of 1920, from 1920 to 1935*. U. S. Public Health Service, Public Health Bulletin No. 252. 74 pp. Washington: Government Printing Office, 1940.
3. *Idem*. *Cancer Mortality in the United States: III. Geographic variation in recorded cancer mortality for detailed sites, for an average of the years 1930-32*. U. S. Public Health Service, Public Health Bulletin No. 257. 81 pp. Washington: Government Printing Office, 1940.

## ADDITIONAL REFERENCES

- Annual Report, Massachusetts Department of Public Health, 1940. (In press.)
- Chadwick, H. D., and Lombard, H. L. A state cancer program. *Am. J. Pub. Health* 28:14-20, 1938.
- Macdonald, E. J. Accuracy of the cancer death records. *Am. J. Pub. Health* 28:818-824, 1938.
- Idem*. The evolution of cancer control in Massachusetts. *Med. Woman's J.* 45:264-270, 1938.
- Macdonald, E. J., and Macdonald, F. A. Evaluation of cancer control methodology. *Am. J. Pub. Health* 30:483-492, 1940.

## THE NATIONAL PHYSICIANS' COMMITTEE\*

STANLEY B. WELD, M.D.†

HARTFORD, CONNECTICUT

AMERICAN medicine no longer enjoys the inviolable right to carry on undisturbed its program of medical care. Although it still commands the respect of its patients, it does not command the unchallenged obeisance of the nineteenth century. This is as it should be. Vast and far-reaching changes are taking place within the social economy of the Nation. Medicine, heretofore considered a profession but now designated by some as a trade, should not expect to escape. One has but to review the accomplishments in the field of medicine alone to realize how rapidly progress has taken place. In one hundred and fifty years, life expectancy in the United States has been raised from thirty-five to sixty-two years, almost 100 per cent. During this same period, smallpox has been robbed of its terror, diphtheria has been conquered, and typhoid fever, tuberculosis, diabetes and a score of lesser ailments have been subjected to control. Today, a child born into an average American home has the prospect of living more than ten years longer than a child born into a similar home in any other great nation of the world. During 1938, American medicine gave to the United States the most favorable

health record of its one hundred and fifty years' history. In this same year, the Nation had the highest general level of health and the lowest death rate ever known in this country or for any comparable number of people anywhere in the world.

The social life of the Nation has undergone a change. On the one hand, widespread unemployment, low farm income and the continuation of conditions of general depression have made it difficult for an ever-increasing number of people to pay for the best medical service and proper hospitalization out of earnings. Concomitant with these conditions, the cost of medical care has increased, owing to many factors involved — not the least of which is the increasing complexity of diagnostic aids. There is at the same time a worldwide trend toward governmental paternalism and the false, suicidal doctrine that the "state" can provide a service and a security that the people cannot otherwise obtain. Most physicians are familiar with families in which the breadwinner, rather than accept a task not to his liking, goes on relief. How this affects the practice of medicine has been too well learned by many a conscientious physician.

Being socially minded, the government at Washington in recent years has attempted to brush

\*Presented at the annual meeting of the New Hampshire Medical Society, Manchester, May 14, 1941.

†Editor-in-chief, *Connecticut State Medical Journal*.

aside the time-worn methods of medical practice, and suggests to the medical profession that it is time for federal control in this field, as in so many others. The Wagner Health Bill was introduced into the Seventy-Sixth Congress, and a health conference was summoned by President Roosevelt. A federal health survey, implemented by the WPA, purported to show the shortcomings of medical care in the Nation—on the heels of a year with the best health record in history! We live in an age of propaganda. This strong arm of the government was drafted to shake the confidence of the public in its physicians as a class. Compulsory health insurance loomed on the political horizon in the last Congress. Its supporters pointed to England, to Germany, to Denmark, to Sweden and to New Zealand as examples of successful compulsory health-insurance programs, making comparisons where comparisons were not only odious but impossible. And riding high on the wave of the whole program of social security, which as yet has a long way to go to demonstrate real security, medical care seemed about to become a political football, kicked off from midfield by its two largest groups of supporters, professors of sociology and economics and well-meaning but misled social workers.

It is true that organized medicine was slow to see the handwriting on the wall. It took small groups in California, in Michigan and in Washington to point the way to more modern methods of better medical care. The physician of the early twentieth century, like his ancestor of the nineteenth, gave little thought to social evolutionary changes in his neighborhood. He was content to go on his daily rounds, caring for all who sought his aid, receiving remuneration where the family exchequer permitted such payment, and caring for the remaining large group, with no reward but the satisfaction of serving his fellow man. He was proud of his labors, worthy of his hire, and gave little if any thought to the discussion of state medicine. An individualist, he saw no reason for relinquishing his claim on his patients so long as they claimed him.

Then, suddenly, the earthquake came, shaking the very foundations beneath him. Assistant Attorney General Arnold secured an indictment against the medical profession for practicing in restraint of trade. It is but fair to recall that the Committee on the Costs of Medical Care in its majority report had advocated group practice of medicine as an aid in extending medical care to a greater number of people. It is also but fair to recognize the efforts of certain groups in this country to establish plans for medical care, based on varying schemes—some good, some bad. But

when the federal government entered the field in open attack against the profession, it failed entirely to realize that the extension of medical care in quantity must include a certain standard of quality to be acceptable to the medical profession.

In November, 1939, the National Physicians' Committee was formed, because it was recognized that for the past twenty-five years there had been evident a trend in political thinking and legislation affecting medicine, medical practice and health. This trend resulted directly in the introduction of the Wagner Health Bill. In May, 1939, the House of Delegates of the American Medical Association had opposed the Wagner Health Bill. Various groups and interests opposing this legislation came to the conclusions that there was real danger in legislation that would result in harmful, revolutionary changes in the system of medicine; that there was a real problem to be solved in connection with the distribution of medical service and hospital facilities; and that the public was uninformed or misinformed about the aims, objects, methods and achievements of American medicine. A group of twelve physicians formed the National Physicians' Committee for the Extension of Medical Service, a nonprofit, nonpolitical organization devoted to maintaining ethical and scientific standards and extending medical service to all the people, and to familiarizing the American public with the facts concerning these methods and achievements.

The American Medical Association has been criticized as reactionary, narrow and obstructive in its actions. Perhaps it has been, but never has it permitted a lowering of the standards of medical care. The association has also been criticized for not carrying on the work now being done by the National Physicians' Committee. It could not. The American Medical Association cannot change its policies on the basis of expediency, or adapt itself to meet emergencies in a short enough time to be effectual. It is exempt from income and social-security taxation as a scientific, educational body, and therefore cannot engage in a campaign within the political gates at Washington. There are many lay groups interested in the solution of these problems from whom the American Medical Association could not expect support.

What has the National Physicians' Committee accomplished to date? First, it has bent its energies on conveying to the public a few factors of such dramatic value that a continuation of the operation would make possible some concept of American medicine's progress and achievements. Let me illustrate how such small beginnings can develop.

In 1939, the Life Saver Company distributed billions of Life Saver candies. This firm started from scratch in a small Bronx garret in 1913 and, through continuous sales effort, built this relatively unimportant item into a total distribution, through chain stores, 800 wholesalers and more than 300,000 retail outlets, of \$4,000,000. Incidentally, E. S. Noble, who did this job and confined his efforts to it, became the first assistant to the Secretary of Commerce. There is practically not a cigar-store or a drugstore counter that does not feature these little candies; there is not a twelve-year-old boy in the United States who does not know what a Life Saver is.

The Wrigley setup is an identical one. The Wrigley Company started from scratch and began selling a not quite respectable commodity. They began fighting the schoolteachers because the children took gum out of their mouths and stuck it under the seats, and the ministers because the undersides of the pews became lined with chewing gum. Ultimately, they imported chicle by the carload and sugar by the boatload until, in 1939, the Wrigley Company grossed \$34,900,000.

The National Physicians' Committee, also starting from scratch, began its effort to inform and educate the public with two *Saturday Evening Post* two-page advertisements that cost \$43,000, with additional costs for art and engraving that brought the total to nearly \$50,000. Industrial firms put up the money to cover the entire cost of these two advertisements. They appeared on June 22 and July 13, 1940.

More important than this was a series of full-page advertisements that appeared from coast to coast in important newspapers. These were patterned after the *Saturday Evening Post* advertisements. This barrage resulted in a statement from Mr. Willkie committing himself to the cause of independent medicine, and a public statement of policy from Mr. Roosevelt prior to his election. All of us are now familiar with Mr. Roosevelt's message at the dedication of the Health Institute in Bethesda, Maryland, when he expressed for the government no intentions of socializing medical practice and lauded the personal relation between doctor and patient that now exists. This, together with the promise to discuss with organized medicine all future legislation affecting the practice of medicine, should at least indicate that concerted effort on our part can bring results.

Following the publicity in the *Saturday Evening Post* and in newspapers from coast to coast, since January 1 there has gone out from the office of the National Physicians' Committee in Chi-

cago a weekly editorial service to more than 12,000 weekly and foreign-language newspapers in the United States. These releases are informative and educational, and should help to correct false impressions of American medicine gained by the public. Very few of these have been published in New Hampshire and Connecticut, but newspaper clippings from publications in February and March indicate 10 to 15 per cent actual publication. This editorial service is still in operation.

On April 4, a federal jury in Washington found the American Medical Association guilty of a "criminal conspiracy to restrain trade." The jury exonerated five officials of the association and fourteen distinguished physicians of the District of Columbia, at the same time convicting the American Medical Association and the Medical Society of the District of Columbia. The verdict is without sense or substance or meaning. Certain basic principles, which in their establishment involved no legal authority, have been challenged. To relinquish them would mean that laymen or lay organizations would have a legal right to provide medical service, that qualified doctors of medicine could no longer determine or influence the qualifications of hospital staffs and physicians with courtesy privileges, and that doctors of medicine would be denied the right to determine or significantly influence the educational standards for medical students, and the nature and quality of intern training. Should this come to pass, the quality and standards of medical service would be placed in jeopardy, and an army of quacks would compete in the open market for the patronage of the ailing and the sick. This decision will be appealed, if necessary, to the Supreme Court of the United States. In the meantime, the public must be informed and made aware of its vital interest in this issue. To this task, the National Physicians' Committee has set itself.

In certain states of the Union, notably California, Michigan, New York, New Jersey and Texas, attempts are being made to provide state-wide service on a prepayment basis under medical-association auspices. The Wisconsin and Minnesota legislatures have passed enabling acts making possible the extension of such a service. Since January 1, 1941, two state societies—Ohio and Tennessee—have sponsored similar legislation. It is this sort of effort that must be encouraged; otherwise the public will be led along the road to compulsory health insurance as outlined in such acts as the Wagner Health Bill and the Epstein Bill.

The program of educating the public concerning a true knowledge of the facts of American med-

icine entails considerable expense. Let us see how the plan was worked out in Houston, Texas. The president of the local medical society appointed a chairman of a committee to co-operate with the National Physicians' Committee. The Houston Medical Society has a membership of approximately 400 physicians. Ten members were selected for the committee. The names, addresses and telephone numbers of all the members were placed on 400 cards, which were divided among the ten committee members. Each member of the committee reached by telephone the physicians assigned to him, explained the nature of the work that had been undertaken by the National Physicians' Committee, and asked them to contribute to the extent that they could without undue sacrifice. Ten dollars was suggested as a reasonable average amount. The president of the society wrote a letter to all the members urging them to co-operate. The committee met each week for a short period until the entire membership had been canvassed. Under the date of November 4, the chair-

man of the committee mailed his check in the amount of \$2,313.50 to the National Physicians' Committee. This plan was effective; it resulted in great good to the members of the Houston Medical Society and can be adapted to any society.

American medicine has been called on to aid in national defense by manning the selective-service medical boards, and by supplying physicians to the Army and the Navy. In addition, Britain has called for 1000 physicians to help fill gaps in its defense program. American medicine is faced with the possibility of drastic changes in its structure. We must not permit the quality of medical service to suffer. The National Physicians' Committee has set itself the task of securing public approval of the standards set up by American medicine and endorsement of only those changes that shall eventuate in improved medical care. The accomplishment of this purpose necessitates the understanding, co-operation and financial support of every county medical society and of the rank and file of the profession.

179 Allyn Street

## THE VALUE OF AUSCULTATION OF THE ABDOMEN IN INTESTINAL OBSTRUCTION

NEIL C. STEVENS, M.D.

WALPOLE, NEW HAMPSHIRE

**A**USCULTATION of the abdomen is a valuable aid in diagnosis of a number of functional and organic conditions of the stomach and intestinal tract. It is particularly useful in cases of intestinal obstruction and acute appendicitis, and four cases of the former condition are cited to illustrate its use.

### CASE REPORTS

**CASE 1.** A 60-year-old farmer complained of severe, cramplike pains in the abdomen. The pain had begun at 4 a.m., waking him out of his sleep, and had continued with increasing severity until examination at 11:30 a.m. The pain was intermittent in character. The patient had vomited twice and had taken an enema, without result. His digestion had always been good; his bowel movements had been regular.

With the exception of the abdomen, physical examination was negative. The abdomen was not distended, although there was a suggestion of rigidity in both lower quadrants. There was marked tenderness at the umbilicus, which was also the area of the maximum intensity of the pain. The temperature was 99°F., and the pulse 85. On auscultation of the abdomen, peristalsis was intermittent. The sounds coincided with the intermittent attacks of pain. The abdomen was completely silent for intervals as long as 2½ minutes. The sounds were rather faint and lasted

not longer than 10 seconds. The spasms of pain were severer than the sounds seemed to indicate. From the character of the sounds and of the pain and from the silent intervals, a diagnosis of intestinal obstruction was made. His immediate removal to the hospital was advised.

On admission to the hospital 2 hours later, the symptoms had not changed appreciably. The white-cell count was 14,000, with 85 per cent polymorphonuclears.

At operation, a volvulus of the middle third of the ileum was found, involving about 20 cm. of the intestine, which was purple in color. Both visible and tactile pulsation of the mesenteric arteries and their branches was evident, and nothing was done except to relieve the obstruction. The patient made an uneventful recovery.

**Comment.** In this case, the onset of pain was at 4 a.m. Operation was performed at 1:30 p.m., an interval of 9½ hours. Peristalsis was present, though faint and infrequent up to the time of operation. The section of the intestine involved was still viable.

**CASE 2.** A 51-year-old farmer began to have pain in the right lower quadrant of the abdomen at about 5 p.m. It came on after finishing a hard day's work in the fields. The pain was colicky to begin with, later on becoming constant. As time went on, it increased in severity. A physician told the patient that he was having an attack of indigestion and gave him some "medicine." The pain persisted



all night, and the patient vomited twice. I saw him the next morning.

Physical examination showed a thin, wiry man who was apparently suffering a good deal of pain. He did not look particularly ill. The temperature was 99.5°, and the pulse 88. The abdomen was not distended, and there was no rigidity. There was considerable tenderness in the right lower quadrant in the region of an old appendectomy scar—the appendix had been removed 6 years before. Peristaltic sounds were present but faint and infrequent.

Because the appendix had been removed and there was no distention or rigidity, I considered it safe to wait until afternoon before deciding what should be done. His wife was told to give him an enema.

At 4 p.m., his condition was much worse, although the pain was not quite so severe. The face was flushed, the respirations were increased, the temperature was 101°F., and the pulse was 100. Peristalsis was entirely absent. The abdomen was distended, and there was extreme tenderness in the right lower quadrant. The patient was taken to the hospital, where an immediate operation was performed.

On opening of the abdomen, there was an outpouring of dark-colored fluid. An area of the ileum, 25 cm. in length, just proximal to the cecum was black. There was a thick band of adhesions originating at the stump of the appendix and attached at its other end to the mesentery of the lower end of the ileum. The devitalized loop of intestine was resected, and an anastomosis was done. The patient died the following day.

*Comment.* This patient was seen 5 years ago, when the value of auscultation of the abdomen was not appreciated in cases of intestinal obstruction. The delay of 8 hours in sending the patient to the hospital was due to the fact that he did not present the cardinal signs of intestinal obstruction. Experience now shows that when the typical signs of obstruction, such as distention, fecal vomiting and a rise in temperature and pulse rate, become evident, it is often too late to save the patient. In this case, it should have been appreciated that the character of the peristalsis indicated advanced obstruction with beginning peritonitis. The sounds were faint and infrequent, a finding that is characteristic of the last stage of viability of the intestine. If the patient had been operated on at that time, he might have survived. Eight hours later the condition was hopeless.

**CASE 3.** A 43-year-old woman complained of abdominal pain. She had been in good health until 2 years previously, when she was operated on for an ovarian cyst. Following this operation, her health had been good until 2 months before I saw her, when she began to complain of vague abdominal pain. One month later, the pain became localized in the left lower quadrant. Three weeks later, the pain increased in severity, and the patient noticed a mass in the left lower quadrant. Three days before I saw her, the mass increased in size, together with an increase in pain and tenderness. On the previous day, the patient had vomited and had been unable to retain anything on her stomach.

Examination showed a long linear scar, 9 cm. in length, extending downward from the navel. The abdomen was greatly distended. A mass, the size of a grapefruit, was palpated in the left lower quadrant. It was extremely tender. Active peristalsis was audible over this mass and sounded close to the ear. The diagnosis of intestinal obstruction was made, and the patient was removed to the hospital.

At operation, many closely matted loops of intestine were found just beneath the abdominal wall and outside the

peritoneum. A rent in the peritoneum, about 8.0 cm. in length and corresponding to the old scar through which the intestines had emerged, was found. The intestines were not badly discolored, and seemed viable. The adhesions were separated, and the tear in the peritoneum was sutured. The patient died on the 3rd day after operation.

*Comment.* In this case, death was probably due to the length of the operation (2 hours), which was occasioned by the attempt to break up innumerable adhesions. At the time of examination, there was some question concerning the nature of the mass, but following auscultation, a definite diagnosis of intestinal obstruction was made.

**CASE 4.** A 37-year-old farmer was seen at the office. He complained of cramplike pains in the abdomen of 2 weeks' duration. For 3 days previously, they had been increasing in severity. His appetite had been poor; he had lost weight and strength.

On physical examination, the abdomen was soft; there was no distention or rigidity; no masses were felt; there was slight tenderness in the left lower quadrant, where most of the pain was located. Peristalsis was active and loud. Rectal examination was negative. The white-cell count was 11,000, with 65 per cent polymorphonuclears.

There did not seem to be any acute condition at the time. The patient was given phenobarbital to quiet down the peristalsis and told to go home and take an enema that evening and the following morning.

The next morning, his wife called up to say that he had had a very uncomfortable night, with a great deal of pain. The enemas had been unsuccessful. He had not vomited, and the temperature was normal. Physical examination was essentially the same as the night before, except that there was complete absence of peristalsis. At intervals over a period of an hour, no sounds were audible. There was no distention, no rigidity and no more tenderness than there had been the previous afternoon.

Because of complete loss of peristaltic sounds, the patient was sent to the hospital with a tentative diagnosis of intestinal obstruction. A surgical consultant saw him soon after arrival and noted no indications of an acute abdomen. The diagnosis was intestinal gripe, and the administration of salts was advised. The patient felt quite well during the afternoon, but had a very bad night. A quarter of a grain of morphine was necessary to stop the pain. The following morning, I saw the patient again, with the surgeon and two other physicians. They agreed that he did not have an acute abdomen and advised keeping him under observation. The blood count, temperature and pulse rate were normal. The tongue was coated. The abdomen was soft; there was no rigidity and only a slight degree of tenderness in the midline below the navel. However, at this time there was slight distention in the suprapubic region. The peristaltic sounds were completely absent.

During the afternoon, the patient complained of a great deal of pain. Toward evening, distention of the abdomen became marked. The temperature was 100°F., and the pulse 105. The peristaltic sounds were completely absent. The face became flushed and drawn. The consulting surgeon was again called and was convinced that there must be some trouble in the abdomen.

At operation, a mass was palpated in the descending colon about the size of a small orange, and proximal to the mass, about 46 cm. of intestine was distended and black. The patient's condition was so poor that nothing more than an enterostomy was attempted; he died the following afternoon.

*Comment* My diagnosis in this case was based on the presence of hypermotility at the first examination, and complete absence of peristalsis noted 14 hours later. Until 3 or 4 hours before operation, it was the only positive physical sign. It preceded the first rise in temperature to 99.5°F by 12 hours. It preceded distention of the abdomen by 36 hours. Neither the pulse rate and blood count—the white cell count just before operation was 10,000, with 77 per cent polymorphonuclears—nor any other physical finding was indicative of a serious abdominal condition.

At the beginning of intestinal obstruction, peristalsis is almost continuous, loud and usually high pitched. The bowel, which is not yet devitalized, is making an effort to overcome the obstruction. A few hours later, peristalsis is still active, but fainter. The musculature of the bowel is becoming fatigued and does not respond so strongly to stimuli. After twelve hours, peristalsis is considerably diminished, and becomes intermittent with intervals of sometimes two minutes between the sounds. By this time, not only is the bowel greatly fatigued, but there is probably a beginning peritonitis, owing to interference with the circulation and the production of toxins, which invade the visceral peritoneum through the damaged wall of the bowel. The last stage, and the one in which the patient most frequently arrives at the hospital, is that of beginning distention, frequent vomiting, and complete cessation of peristalsis; at operation, a section of the bowel is found to be gangrenous.

My experience leads me to believe that, so long as peristaltic sounds are heard, the bowel is not completely devitalized and that the chance for recovery following operation is very good. The

more active the peristalsis preceding operation, the better the chances for recovery. After some experience in auscultation, one can predict with considerable accuracy the condition and color of the bowel that will be found at operation. If peristalsis is active and loud, the section of the bowel involved will be congested and red or pink. If the peristalsis is faint and intermittent, the bowel will be purple. If peristalsis is entirely absent, the bowel will be black. In all but the last stage, the circulation can probably be restored if the obstruction is relieved.

Cessation of peristalsis seems to depend on infection or irritation of the peritoneum. It most commonly occurs in such conditions as intestinal obstruction, acute appendicitis (before and at the time of rupture) and rupture of a gastric and duodenal ulcer. In cases of retrocecal appendicitis, peristalsis does not stop, because the appendix lies outside the peritoneal cavity. Cessation of peristalsis also depends on the continued spread of peritonitis. When peritonitis becomes localized, as in cases of walled-off inflamed appendixes, peristalsis begins again, and may be hyperactive if there is partial or complete obstruction.

#### CONCLUSIONS

Auscultation of the abdomen is a valuable method of diagnosis in cases of early intestinal obstruction.

The condition and color of the bowel can often be predicted by the frequency and character of the sounds.

all night, and the patient vomited twice. I saw him the next morning.

Physical examination showed a thin, wiry man who was apparently suffering a good deal of pain. He did not look particularly ill. The temperature was 99.5°, and the pulse 88. The abdomen was not distended, and there was no rigidity. There was considerable tenderness in the right lower quadrant in the region of an old appendectomy scar—the appendix had been removed 6 years before. Peristaltic sounds were present but faint and infrequent.

Because the appendix had been removed and there was no distention or rigidity, I considered it safe to wait until afternoon before deciding what should be done. His wife was told to give him an enema.

At 4 p.m., his condition was much worse, although the pain was not quite so severe. The face was flushed, the respirations were increased, the temperature was 101°F., and the pulse was 100. Peristalsis was entirely absent. The abdomen was distended, and there was extreme tenderness in the right lower quadrant. The patient was taken to the hospital, where an immediate operation was performed.

On opening of the abdomen, there was an outpouring of dark-colored fluid. An area of the ileum, 25 cm. in length, just proximal to the cecum was black. There was a thick band of adhesions originating at the stump of the appendix and attached at its other end to the mesentery of the lower end of the ileum. The devitalized loop of intestine was resected, and an anastomosis was done. The patient died the following day.

*Comment.* This patient was seen 5 years ago, when the value of auscultation of the abdomen was not appreciated in cases of intestinal obstruction. The delay of 8 hours in sending the patient to the hospital was due to the fact that he did not present the cardinal signs of intestinal obstruction. Experience now shows that when the typical signs of obstruction, such as distention, fecal vomiting and a rise in temperature and pulse rate, become evident, it is often too late to save the patient. In this case, it should have been appreciated that the character of the peristalsis indicated advanced obstruction with beginning peritonitis. The sounds were faint and infrequent, a finding that is characteristic of the last stage of viability of the intestine. If the patient had been operated on at that time, he might have survived. Eight hours later the condition was hopeless.

**CASE 3.** A 43-year-old woman complained of abdominal pain. She had been in good health until 2 years previously, when she was operated on for an ovarian cyst. Following this operation, her health had been good until 2 months before I saw her, when she began to complain of vague abdominal pain. One month later, the pain became localized in the left lower quadrant. Three weeks later, the pain increased in severity, and the patient noticed a mass in the left lower quadrant. Three days before I saw her, the mass increased in size, together with an increase in pain and tenderness. On the previous day, the patient had vomited and had been unable to retain anything on her stomach.

Examination showed a long linear scar, 9 cm. in length, extending downward from the navel. The abdomen was greatly distended. A mass, the size of a grapefruit, was palpated in the left lower quadrant. It was extremely tender. Active peristalsis was audible over this mass and sounded close to the ear. The diagnosis of intestinal obstruction was made, and the patient was removed to the hospital.

At operation, many closely matted loops of intestine were found just beneath the abdominal wall and outside the

peritoneum. A rent in the peritoneum, about 8.0 cm. in length and corresponding to the old scar through which the intestines had emerged, was found. The intestines were not badly discolored, and seemed viable. The adhesions were separated, and the tear in the peritoneum was sutured. The patient died on the 3rd day after operation.

*Comment.* In this case, death was probably due to the length of the operation (2 hours), which was occasioned by the attempt to break up innumerable adhesions. At the time of examination, there was some question concerning the nature of the mass, but following auscultation, a definite diagnosis of intestinal obstruction was made.

**CASE 4.** A 37-year-old farmer was seen at the office. He complained of cramplike pains in the abdomen of 2 weeks' duration. For 3 days previously, they had been increasing in severity. His appetite had been poor; he had lost weight and strength.

On physical examination, the abdomen was soft; there was no distention or rigidity; no masses were felt; there was slight tenderness in the left lower quadrant, where most of the pain was located. Peristalsis was active and loud. Rectal examination was negative. The white-cell count was 11,000, with 65 per cent polymorphonuclears.

There did not seem to be any acute condition at the time. The patient was given phenobarbital to quiet down the peristalsis and told to go home and take an enema that evening and the following morning.

The next morning, his wife called up to say that he had had a very uncomfortable night, with a great deal of pain. The enemas had been unsuccessful. He had not vomited, and the temperature was normal. Physical examination was essentially the same as the night before, except that there was complete absence of peristalsis. At intervals over a period of an hour, no sounds were audible. There was no distention, no rigidity and no more tenderness than there had been the previous afternoon.

Because of complete loss of peristaltic sounds, the patient was sent to the hospital with a tentative diagnosis of intestinal obstruction. A surgical consultant saw him soon after arrival and noted no indications of an acute abdomen. The diagnosis was intestinal gripe, and the administration of salts was advised. The patient felt quite well during the afternoon, but had a very bad night. A quarter of a grain of morphine was necessary to stop the pain. The following morning, I saw the patient again, with the surgeon and two other physicians. They agreed that he did not have an acute abdomen and advised keeping him under observation. The blood count, temperature and pulse rate were normal. The tongue was coated. The abdomen was soft; there was no rigidity and only a slight degree of tenderness in the midline below the navel. However, at this time there was slight distention in the suprapubic region. The peristaltic sounds were completely absent.

During the afternoon, the patient complained of a great deal of pain. Toward evening, distention of the abdomen became marked. The temperature was 100°F., and the pulse 105. The peristaltic sounds were completely absent. The face became flushed and drawn. The consulting surgeon was again called and was convinced that there must be some trouble in the abdomen.

At operation, a mass was palpated in the descending colon about the size of a small orange, and proximal to the mass, about 46 cm. of intestine was distended and black. The patient's condition was so poor that nothing more than an enterostomy was attempted; he died the following afternoon.

relieved. During this episode, he had a temperature of 102.5°F., and there was vomiting but only slight nausea.

The patient was admitted to a Boston hospital, where he was seen by a distinguished internist on December 24. The admission temperature was 101.5°F., after which there was, for 4 days, a gradual fall to normal. There was also slight leukocytosis (white-cell count, 11,800), with 77 per cent polymorphonuclear neutrophils. Subsequent white-cell counts were 8750 and 6650. The red-cell count was 4,360,000, with a hemoglobin of 80 per cent (Sahli). The carbon dioxide combining power of the plasma was 47 vol. per cent, on the 7th hospital day. Roentgenograms of the pelvis and left hip were interpreted as showing no bony

school, and this had healed promptly and without complications. He had suffered no other injuries of note, although in playing football he had undergone considerable roughing. He had had hay fever every August since the age of 12. The family history revealed that his mother had had a tuberculous fallopian tube removed, and that a paternal uncle had died, at the age of 30, from embryoma of the testis.

Physical examination showed a very well-developed and well-nourished young man. The only abnormal findings were those about the left hip: generalized protective muscle spasm, demonstrated by attempted rotatory movements of the thigh and by the straight-leg-raising test.



FIGURE 1. Roentgenogram of Pelvis (February 8, 1939), Showing a Rarefied Area in the Left Ilium adjacent to the Acetabulum.

abnormalities. It was the consultant's opinion that some infectious process was subsiding, and the discharge diagnosis was "iliopsoas spasm, cause unknown."

After 10 days' convalescence at his home, the patient attempted to return to school, against his physician's advice. Shortly, he suffered another attack of pain, not so severe as the preceding seizure but requiring morphine on 2 successive nights. After a week of comfort, there was recurrent pain, and then a short free interval before a 3rd paroxysm. During this attack, on February 7, 1939, the patient was admitted to the Joseph H. Pratt Diagnostic Hospital. He stated that on the night before admission he had suffered the most intense recent pain, and had received several ¼-gr. doses of morphine by mouth, but, even though he was still in considerable distress, he believed that the current attack was subsiding.

It was learned that the patient had been a rather delicate child but was afterward healthy and vigorous. His tonsils and adenoids had been removed when he was 6 years old. At the age of 9, he had had lobar pneumonia, and during the illness an appendectomy had been performed. He had broken his left thumb in a scuffle at

There was no evident tumefaction or inflammation externally, but by rectal examination there were fullness and point-tenderness in the left pelvic wall. The patient complained of pain in the left groin during this examination. Another point of tenderness was found deep in the left buttock centrally.

The temperature was 101°F.

The blood showed a red-cell count of 4,750,000 with a hemoglobin of 74 per cent (Sahli), and a white-cell count of 9300 with 69 per cent polymorphonuclear cells and 2 per cent band forms. The sedimentation rate was somewhat elevated: 24 mm. in one hour, by the Westergren method. The urine contained no albumin or Bence-Jones protein. The blood phosphatase was 1.0 Bodansky unit. A roentgenogram of the pelvis (Fig. 1) showed an oval-shaped area of bone rarefaction in the left ilium adjacent to the acetabulum. The cortex in this region was thinned, and there was a faint outline of a soft-tissue mass projecting into the pelvis at a point beside the rarefied bone. In a review of the previous roentgenograms (taken in December, 1938), a slight but definite rarefaction could be seen. The findings were considered highly suspicious of

primary malignant bone tumor; the diagnoses of Ewing's sarcoma and lymphoblastoma were considered. However, on the assumption that osteomyelitis was the likely morbid process, an orthopedic surgeon decided on osteotomy.

At operation on February 9, the left ilium was entered posteriorly, and not pus but a dark, reddish, fleshy tissue was found. This had already invaded the gluteal musculature. Frozen sections proved the diagnosis of sarcoma. The pathologist's report was, "atypical Ewing's sarcoma, with well-formed reticulum." Tumor cells were seen within the lumina of blood vessels. The tissue also showed changes of recurrent inflammation.

Following the operation, there was extreme pain for 2 days, only fairly well controlled by maximum doses of dilaudid. On February 14, the patient was transferred to the Collis P. Huntington Memorial Hospital, where irradiation therapy from the million-volt machine was started. This was directed over the left pelvis, from all sides (15 x 15 cm. field), 200 r daily for 4 days, then 300 r daily for 14 days. There was relief from pain after the third day of treatment, and there was only slight roentgen sickness in spite of the large amount of radiation. Toward the end of February, the patient suffered an attack of what seemed to be grippe, with fever, cough and sore throat. When he was discharged on March 3, he had received a total of 3600 r. By March 25 (during ambulatory treatment) he had received 1500 r in addition, a grand total of 5100 r.

In March and April, the patient seemed to be making a progressive recovery. He was eating heartily and gaining weight. He was able to return to medical school but used crutches to avoid trauma to the left hip. He even played ball by hopping on the unaffected leg. At a follow-up visit on March 21, his physician found, on rectal examination, no remaining tenderness over the rami of the left pelvic bones but some soft-part thickening just posteriorly. The red-cell count was 4,010,000 with a hemoglobin of 68 per cent (Sahli), or 9.5 gm. per 100 cc. During these months, the blood sedimentation rate (Westergren) was normal, 4 and 8 mm. in one hour. The blood phosphatase was 1.25 Bodansky units.

On April 29, after 2 months of complete freedom from pain, the patient noticed a dull ache in the left shoulder; this had begun simply as an uneasiness noted during a medical-school examination. It became more pronounced during the evening, and through the next day, the pain increased steadily and kept him awake in the night. It was centered at the head of the humerus and was of a deep, boring type, with constant aching. By the 2nd day, the pain was severe and throbbing. The patient recognized that its character was identical with that of the paroxysmal pain he had suffered in his hip. There was no interference with motion of the left arm, and use of it did not increase the pain, but there was slight pain on complete inward rotation of the arm. The patient was admitted to the Outpatient Department of the Huntington Hospital, where a roentgenogram was interpreted as showing a small area of calcification in the proximal end of the left humerus. Daily irradiation was administered from May 1 through May 9, again with the high-voltage machine, a total of 1700 r to the left shoulder being given. The pain seemed to be increased in the evening after the first treatment, and on the 2nd day of irradiation there was severe nausea, but before the third treatment the pain was much lessened. By the 4th day, the patient was so much improved that he was able to make a trip to New York City for an interview about his proposed internship there.

On May 9, the patient was readmitted to the Pratt Hospital. Although he had had only slight residual

had noticed, a day or so before entrance, discomfort in the right upper chest anteriorly, associated with other pain of rather vague but moderately severe character, gradually centering about the 3rd dorsal vertebra. The chest pain had awakened him in the night before entrance, and at that time seemed to be aggravated by deep respiration. On admission to the hospital, the relation to respiration was not so evident, and the discomfort seemed to be decreasing. Physical examination showed the patient to be in apparent good health, and an increase in weight since the February admission was apparent. There were no abnormal signs in the chest, and a roentgenogram of the thorax was entirely normal. The left shoulder showed some erythema of the skin following the recent course of irradiation, but was otherwise apparently normal. The operative scar across the left buttock was well healed; there was no induration or tenderness. There was slight pigmentation about the left hip from the irradiation in February, and a lack of hair in this area. The muscles of the left thigh and leg were flabby, and there was some wasting as compared with the firm muscles of the right leg. There was an increased patellar-tendon reflex in the left leg, and slight, transitory ankle clonus. The thigh could be rotated without discomfort. The hip joints seemed equal in motion. There was no Lasègue's sign on either side. The hemoglobin determination was 78 per cent (Sahli), and the white-cell count was 5300. The sedimentation rate was normal (10 mm. in 1 hour, 21 mm. in 2 hours) by the Westergren method. Roentgenograms of the whole skeleton were made at this time. The lesion in the left ilium appeared to be somewhat filled in by reparative bone. There was nothing in the remaining parts of the skeleton to suggest metastasis. Repeat films of the left humerus showed normal bone detail in the region of the greater tuberosity. The highest temperature was 98.8°F. It was decided that the clinical evidence for a new lesion in the upper left humerus was convincing, but that the vague and nonprogressive symptoms related to the upper back and right chest were of less significance and were possibly caused by "overawareness" on the part of the patient.

During May, there were hints of continuing disease. The left shoulder was still affected, and was painful when jarred in games of catch. The patient was less vigorous and less enthusiastic. He had vaguely defined pains in the neck, back and chest. In filing papers, he had to stop frequently because of backache. There was once an alarming, sudden grating sensation on flexing the back, and a physician was consulted, but no abnormality was demonstrated. Appetite was poor, and insomnia became frequent. However, it was pointed out to the patient that he had repeatedly normal temperature readings, and a normal sedimentation rate and leukocyte count; it was explained to him how easily undue apprehension, and frustration of his strong desire to go ahead with his internship in spite of the dire outlook, might cause his pains and ill-health, through the mechanism of psychoneurosis. Thus, a regrettable delay in treatment ensued.

On May 28, the patient was readmitted to the Pratt Hospital, looking haggard and complaining of discomfort in the upper dorsal spine, associated with interscapular aching and muscular tenderness; point tenderness was found over the 3rd dorsal vertebra. Vague occipital headache was present. There was also discomfort at the lumbosacral junction. Another point of tenderness was discovered on the right 11th rib, in the midaxillary line: no friction rub could be detected, but there was slight soreness associated with deep respiration. Roentgenograms

showed right pleural metastases, although the spine appeared to be normal. The patient had a temperature of  $100.2^{\circ}\text{F}$ , a white-cell count of 8750, a relative polymorphonuclear leukocytosis (91 per cent) and some shift to the left, and an increase of the sedimentation rate by daily, serial tests. The serum phosphatase (alkaline) was still low—0.85 Bodinsky unit. Focal roentgen ray therapy was reinstituted. The patient was taken daily by ambulance to the Huntington Hospital for treatment by the million volt machine.

The episode that made rehospitalization necessary was the first of a series of six, which took place at fortnightly intervals throughout the summer (Fig 2). Every episode was announced by new pains, as well as by malaise and rigors, and was confirmed by a striking rise in the sedimentation rate and by fever (of slight to moderate de-

pernicious type preventing proper fluid and caloric intake). Nausea was not alleviated by intravenous glucose and saline solutions, nasal oxygen or peroral and parenteral thiamin chloride.

The patient was taken back to the Pratt Hospital in mid June, at a time of striking improvement. For a few days, his progress was encouraging. Roentgenograms indicated complete disappearance of the pleural lesions; it seemed that the therapeutic weapon was competent. Yet pleural discomfort was still present, and when the patient coughed he was conscious of tender points along the spine.

The next flare up was predicted by throbbing headache which developed during the last week of June and reached its acme by the 2nd day of July. It was left-sided over the eye. A roentgenogram of the skull (Fig 3) showed

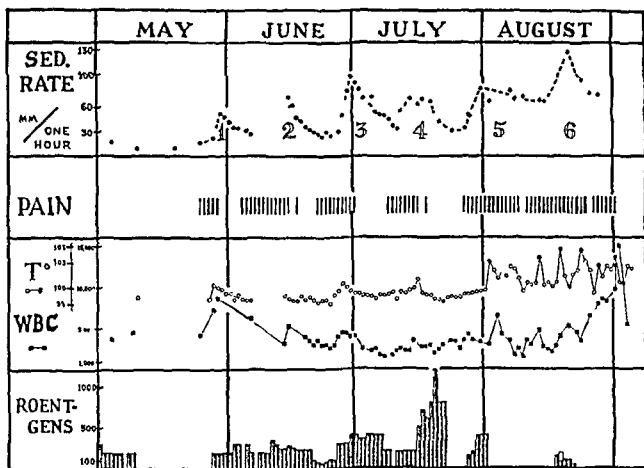


FIGURE 2 Chronological Chart of Sedimentation Rates, Pain, Temperatures, White Cell Counts and Radiation Therapy

gree) and rise in the leukocyte count. Irradiation was increased at every exacerbation, and the bombardment was followed, more or less promptly, by relief from pain and by subsidence of the fit of illness. As the vital signs reapproached normal ranges, and the sedimentation rate lessened steadily, there occurred regularly a period of comfort and a betraying appearance of marked improvement. This was always short lived, however, new pains soon arrived to announce the next cycle.

The first period of relief, in the early days of June, gave way to a paroxysm of distress about the spine—a glass brick, due to alarming muscular spasticity, was evident. There was a return of pleuritic pain and later a friction rub, this time at the left costal border, along with a point of tenderness. Marked prostration signified the severity of the attack; morphine was required for the mounting pain. The patient was transferred to the Huntington Hospital for intensive irradiation. In spite of this treatment, he had much pain for several days—as well as exhausting nausea and vomiting, which were attributed to the heroic therapy. Roentgen sickness was from then on an enervating complication. The vomiting was of a

scattered lesions in the calvarium. There was slight epistaxis. It was necessary to direct irradiation to the head and this entailed interruption of the program of systematic coverage then in progress. After the second retreatment to the head the patient was decidedly more comfortable. The headache returned after another day, in spite of continued irradiation. As in previous attacks, other areas were excited, and throbbing pain developed along the right pelvic brim (Local hyperesthesia alone had been noted 2 weeks earlier, at an analogous time in the preceding episode). There was also intense pain in the lower left thigh. At length improvement was attained and in early July there was a series of days without pain and with only the relentless x-ray nausea.

The fourth episode in the generalization of the disease occurred in mid July, and was marked by pain in the left arm and, shortly thereafter, by severe pain in the right shoulder and arm and in both thighs. Neither at this time nor, in fact, during any episode did pain occur in the extremities distal to the elbows and knees. At this exacerbation the patient experienced symptoms rumored in association with the original lesion: point tender

ness in the left buttock and paresthesia in the left groin and about the hip. It had to be admitted that roentgen-ray therapy was being used for its palliative effect alone, and that more of the noxious irradiation than the weakened condition warranted would be needed for the widespread lesions.

There was about a week of some comfort (toward the end of July) before the fifth episode began. Pain was localized once more in the left hip and groin, in the right shoulder and neck, associated with marked lameness of the musculature, and in the right chest, with respirations; point tenderness in the 5th rib, anterolaterally, could be elicited. A short time later, pain was also

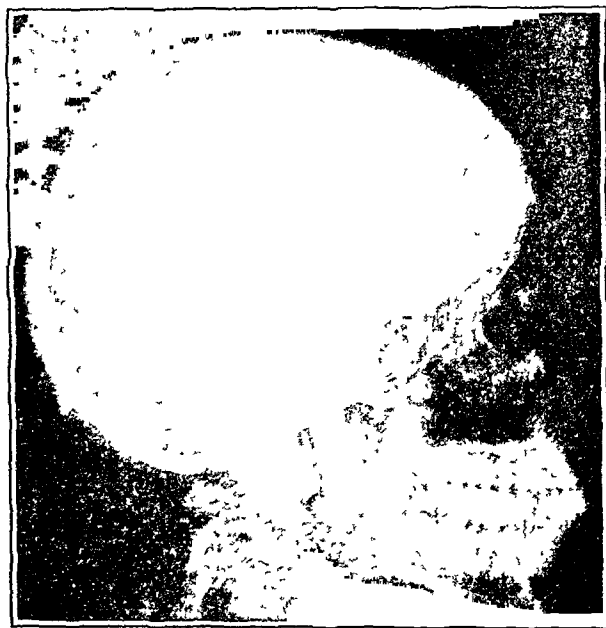


FIGURE 3. Roentgenogram of Skull (June 24, 1939), Showing Scattered Metastatic Lesions in the Calvarium.

localized along the left costal border anteriorly (aggravated by hiccup), in the occiput and across the back at the level of the 12th dorsal vertebra.

On August 1, the patient was transferred to the Huntington Hospital because it was not decided to begin treatment with a purified Coley's toxin (concentrated filtrate of *Bacillus prodigiosus*). He had become unnaturally lean. At the time of transfer, the fifth episode was near its height, the pain being most marked in the left iliac crest and in the right chest. On August 2, the first dose of filtrate, given intramuscularly, was followed in 3 hours by a severe chill, a sharp fever of 103°F. and convulsive vomiting. After 2 weeks, additional and successively stronger doses were given every 4 or 5 days—six injections in all. Intravenous barbiturates alleviated the vomiting.

A brief respite on August 10 marked a point analogous with the time of relief experienced during subsidence of previous episodes. But prompt return of back pain (dorso-lumbar and cervical) indicated the proximity of the ensuing spell. There were warnings also in occipital and left frontal headaches, which increased and became throbbing in character during mid-August, and in anesthetics of the left lower lip, adjoining skin and adjacent buccal mucosa. In addition, on August 16, diplopia appeared; there was a left external rectus palsy. During these days, pain was again present in the left iliac crest, in the lower

right chest laterally and in the lumbar region. A striking spasticity of the left upper rectus muscle of the abdomen, which had been noted in conjunction with the left costal-border distress early in the month, reappeared. Very severe back pain was precipitated by an injection of filtrate on August 19. A continuation of the mid-August seizure was exhibited by distressing pleuritic pain, with palpable friction-rubs, first in the left side and then in both. The throbbing left-sided headache was recurrent; there was a discharge of bloody, tenacious mucus from the left nostril. Associated with left iliac pain, the adjacent femoral musculature showed continual and painful spasm, with later local pitting edema and a peculiar doughy consistence.

Roentgenograms in mid-August demonstrated apparently clear lung fields. There was erosion of the left iliac crest; the hip joints were normal; the site of the original tumor appeared to be somewhat more filled in by reparative bone. In the skull, no abnormal changes could be detected in the sella turcica, petrous ridges and paranasal sinuses; the rarefied foci throughout the cranium were not so sharply defined as formerly.

Toward the end of August, and at a time of progressively slowing erythrocyte sedimentation, the patient became more vigorous and had several comparatively comfortable days. Morphine was required, nevertheless, at regular intervals, and even in large doses did not completely relieve distress. There was excruciating pleuritic pain, and all the other familiar pains were revived, following a fifth injection of filtrate on August 28.

Terminally, there was respiratory embarrassment. Brief periods of hyperpnea and polypnea began to appear about a week before death. On September 3, the patient had noted marked air-hunger in the early morning, and this became his main concern in the forenoon. A transfusion did not lessen the dyspnea. The breathing was of the Kussmaul type, with terminal expiratory effort. A severe acidosis was indicated by a plasma carbon dioxide combining power of 13 vol. per cent. Examination of the chest indicated accumulating pleural fluid, especially on the right side. A marked bleeding tendency was apparent at every hypodermic injection; the bleeding time was prolonged to 9 minutes; platelets appeared to be much reduced. By the use of intravenous sodium bicarbonate, the plasma alkalinity was increased to a normal level. Yet the patient recognized the fact that the dyspnea was not commensurately improved. He died on September 5, a year after the onset of symptoms.

*Autopsy.* Except for advanced infiltration of the lungs, there was a striking absence of tumor in the viscera, and the skeleton was shown to be the chief depository. The brain, liver, spleen, kidneys, heart and intestine were essentially normal. A large amount of tumor was found in the pelvis adjacent to the original lesion; it had infiltrated the adjoining musculature. The bulk of this tumor was necrotic, and there were many hemorrhages centrally in the larger nodules. The tissue was grayish and softened, with the appearance of brain tissue.

There were lesions arising from the ribs that projected into the parietal pleura on both sides, and the surface of the left diaphragm was covered with tumor nodules. The vertebrae showed diffuse sarcomatous infiltration, especially advanced in the 12th dorsal vertebra. In the base of the skull, the left petrous bone and the sphenoid and left ethmoid sinuses contained tumor; the calvarium, on transillumination, showed spotty infiltration. No tumor could be found in the upper left humerus (the site of the earliest secondary deposit). The mediastinal and pelvic lymph nodes contained tumor. There was bloody pleural

fluid in both sides. The bony lesions were destructive, new bone was not present.

Microscopically, the lesions were typical of those of Ewing's sarcoma (Fig. 4).

**Radiotherapeutic note.** According to the roentgenologist (Dr. Richard Dresser), from the radiotherapeutic standpoint, several interesting observations were made in this case. Roentgen rays approaching in average wave length the gamma rays of radium were employed. Although huge amounts of radiation were given, the skin showed remarkably little reaction, and at no time was it necessary to halt therapy because of damage to the superficial structures. Although the patient was by no means free from roentgen sickness, the general untoward reaction to the superhard radiation was less than would have been antici-



FIGURE 4 Photograph of a Section of the Tumor.

pated from corresponding doses of 200 kilovolt roentgen rays. The clinical response to radiation was essentially the same as that observed in a number of other such cases that is, a brief respite from symptoms with general improvement, only to be followed by metastatic manifestations and a progressively downhill course. Although at autopsy much tumor tissue was found at the site of the primary lesion, it is difficult to say how much of this was the original growth and how much metastatic disease. It is well known that the secondary deposits of any growth are prone to be less radiosensitive than the original neoplasm.

#### COMMENT

**Mortality statistics.** Ewing,<sup>5</sup> in 1921, singled out this neoplasm of bone as an entity because of its response to radiotherapy (radium). Its incidence is given as between 10 and 15 per cent of malignant tumors of bone.<sup>6</sup> Its pre-eminent malignancy<sup>3</sup> is attested by the published reviews of series of cases. In 1926, Connor<sup>2</sup> found 11 per cent "cures" in 54 cases (52 from the Registry of Bone Sarcoma and 2 from the Massachusetts General Hospital). In 1930, Copeland and Geschickter<sup>7</sup> reported that 86 of 99 patients had died, but that 13 were apparently well: 3 for four and a half to five and a half years, and 8 for three to five years. In 1939, Geschickter and Maseritz<sup>8</sup> gave a figure

of 94 per cent fatalities in a group of 135 cases. Meyerding<sup>1</sup> has been able to demonstrate a patient who was well five years after biopsy and irradiation, and another who showed no recurrence fifteen years after curettage, irradiation, Coley's toxin and, finally, amputation. In 1938, Meyerding<sup>9</sup> also added to the literature a ten-year cure effected by means of Coley's toxin in addition to irradiation therapy, and an eleven-and-a-half-year cure by amputation followed by irradiation. Desjardins, Meyerding and Luddy<sup>10</sup> observed 6 patients of a series of 24 so treated who were alive two to twelve years after treatment by irradiation alone. On the other hand, W. B. Coley<sup>11</sup> stated, in 1935, that no five-year cures of Ewing's tumor of the long bones were effected by irradiation alone, in either his series of 50 patients or in the group of 100 cases in the Registry. He<sup>12</sup> had pointed out earlier that half the five-year cures in the Registry had had his toxin as part of the therapy. It is arresting to read that advanced and inoperable cases have thus been reclaimed: 12 of 22 inoperable patients (6 treated by toxins only, and 6 by toxins in addition to x-ray) have been well for five to seventeen years. In 1931, W. B. Coley<sup>13</sup> presented 6 cases apparently cured by toxin and radium therapy after extensive metastases. The case presented by Christian and Palmer<sup>14</sup> is an example of amazing therapeutic triumph, but the course was leisurely and not fulminating like that of the more fatal tumors. Simmons<sup>15</sup> has pointed out that the Registry contains no case of a cure of bone sarcoma by irradiation alone. In 47 cases of bone sarcoma at the Massachusetts General Hospital from 1920 to 1932, inclusive, he found 8 cases of Ewing's sarcoma, all of which were fatal; 4 had been treated by amputation and 4 by irradiation, and these had shown the regular but only temporary response. Both he and B. L. Coley<sup>16</sup> stated recently that they have not observed a single authenticated case of a five-year cure.

**Therapeutic procedure.** Simmons<sup>17</sup> believes that there is some hope if radical amputation can be carried out. Copeland and Geschickter<sup>7</sup> consider radical surgery combined with irradiation to offer most in therapy. Geschickter and Maseritz<sup>8</sup> approve biopsy, after a preceding roentgen therapeutic test, to be followed by surgery—resection of shaft, or amputation in the weight-bearing bones of the lower extremity. B. L. Coley<sup>16</sup> urges that biopsy be done before irradiation because of the distorting effect of roentgen rays on the cells, and the ensuing difficulty in microscopical diagnosis. W. B. Coley<sup>11</sup> agrees that amputation is not to be spared as a therapeutic necessity, and



has said that irradiation should be depended on only in the inoperable case. He urges biopsy, if the diagnosis cannot be made without it. Prolonged toxin therapy is advised, to be given adjuvantly in surgical intervention. Meyerding<sup>9, 17</sup> insists that early irradiation is the method of choice.

*Prognosis.* It was observed by Ewing<sup>18</sup> that the mortality is higher in younger patients. He estimated the duration of the disease to be from one to three years. Twelve months is given as the average duration of symptoms before the patient is seen. Copeland and Geschickter<sup>7</sup> state that the average duration of symptoms preoperatively in patients who live is twenty months, whereas in the fatal cases it is only six months. Thus, it is possible to predict the course by the time of development of severe symptoms. Simmons<sup>15</sup> has stated that the prognosis in bone sarcoma depends more on the degree of differentiation of tumor cells than on any other factor. A corollary conclusion is that, once metastases appear, the outlook is grave, regardless of the type of therapy.

*Proper clinical attitude.* It is well to remember that the discouraging statistics contain a considerable element of delayed diagnosis. Desjardins et al.<sup>10</sup> state that, in a group of 42 cases of endothelioma of bone, an accurate clinical diagnosis was made in only 9 cases. Other contributory reasons for the many failures might be found in poor roentgenography and inadequate irradiation. Even if it must be admitted that few of the tumors have been permanently controlled, it does appear that there was effectual intervention in the favorable cases. The striking radiosensitivity of Ewing's tumor seems to present prima-facie evidence for an eventual control by roentgenotherapy. Yet the strong suggestions of underlying constitutional nature, as well as the inflammatory character of the growth, enliven the hope for successful use of a perfected toxin. Connor's<sup>2</sup> exhortation may well be repeated after fifteen years: the disease "should not be looked upon as hopelessly fatal from the start. . . . A consistent and persistent attack . . . will frequently control it temporarily, and . . . in a number of cases permanently."

#### CONCLUSIONS

The clinical story in Ewing's sarcoma of bone reflects the appearance and progress of a recognizable pathologic entity, and is of decided importance in diagnosis and treatment, especially in cases in which the lesion is hidden or the process is histologically and roentgenographically obscure. The salient clinical characteristics are: insidious onset, regular alternation of episodes of pain and periods of comfort, and progressive intensifica-

tion. The last is a feature of the component episode, as well as of the total course.

Early diagnosis is adjured because the tumor possesses unique radiosensitiveness, and treatment must be instituted prior to generalization of the disease.

The natural history of the tumor is of value in avoiding the common, erroneous diagnosis of osteomyelitis, which is strongly suggested by the inflammatory signs. Fever and leukocytosis during episodes may be striking.

On the other hand, technical signs of active disease may be so slightly suggestive that the physician departs from consideration of a morbid process and begins to suspect emotional difficulties.

Such an interpretation of events encourages delay in treatment. The patient's recognition of the recurrence of familiar pain should be given full credence.

The roentgenogram is not a dependable index of integrity of bone. Lesions undeniable from the clinical standpoint may remain unvisualized until an advanced stage.

Although the factor of hereditary predisposition to neoplasm is suggested by the incidence of embryoma of the testis in an uncle, there was in the case presented no indictable precipitating cause, such as specific trauma.

This case supports the idea that prognosis is chiefly dependent on the degree of malignancy. The fulminating character of the neoplasm in this patient was indicated by the rapid evolution and resolution of the disease. The growth-behavior of the tumor is the fundamental criterion in prognosis. To say that the early appearance of secondary lesions removes a patient from the group of those who may get well is simply to admit the primacy of this concept.

The effectiveness of irradiation was demonstrated in this case by prompt subsidence of symptoms and by reinstitution of apparent health for two and a half months. Since after this period, however, secondary neoplastic foci appeared, it must be concluded either that metastasis had already occurred before irradiation of the ilium or that dissemination proceeded afterward, from radioresistant cells in the parental tumor.

In spite of almost relentless irradiation in heavy dosage, evidences of insufficiency of the bone-marrow did not appear until the terminal days of cachexia. Even then, an abundant polymorphonuclear leukocytosis was possible.

The metastatic phenomenon of predilection for bone indicates a favoring milieu there, in contrast with visceral inhospitality.

In the case presented, it was striking that at the times of reactivation, and when new lesions were appearing, old sites of metastasis became painful again. Such manifestation of a general, co-ordinated development was corroborated in the cycle of variation in rate of blood sedimentation, which took place with regularity in spite of irradiation, toxin therapy and progressing anemia. Furthermore, the timing of cycles during the stage of generalization was apparently the same as that when the primary tumor was evolving. This maintenance of a basal rhythmicity throughout the whole active course points to a supervisory regulation of growth in the constellation of tumors, and reflects the interplay of neoplastic increment and systemic readjustment. One gains a larger, biologic concept of the disease if one considers the tumors, not as independent lesions, but as homologous neoplasms obeying an intermittent irresistible force.

5 Bay State Road

## REFERENCES

1. Kolodny, A. Bone sarcoma: osteogenic sarcoma. *Surg., Gynec. & Obst.* Supp. 1 44 26-128, 1927.
2. Connor, C. L. Endothelial myeloma. *Ewing Arch. Surg.* 12:789-829, 1926.
3. Coley, W. B. Endothelial myeloma or Ewing's sarcoma. *Pathology* 16 627-656, 1931.
4. Meyerding, H. W. The clinical and surgical aspects of bone tumors. *Radiology* 26 417-423, 1936.
5. Ewing, J. Diffuse endothelioma of bone. *Proc. New York Path. Soc.* N. S. 21:17-24, 1921.
6. Boyd, W. *A Text Book of Pathology*. Third edition. 1064 pp. Philadelphia: Lea & Febiger, 1938. Pp. 989-992.
7. Copeland, M. M., and Geschickter, C. F. Ewing's sarcoma: small round cell sarcoma of bone. *Arch. Surg.* 20 246-304, 1930.
8. Geschickter, C. F., and Materniz, I. H. Ewing's sarcoma. *J. Bone & Joint Surg.* 21:26-39, 1939.
9. Meyerding, H. W. Diagnosis and treatment of Ewing's sarcoma. *Tr. West. S. A.*, 1938. Pp. 183-204.
10. Desjardins, A. U., Meyerding, H. W., and Leddy, E. T. Radiotherapy for endothelioma of bone. *Am. J. Roentgenol.* 38:344-351, 1937.
11. Coley, W. B. Endothelial myeloma or Ewing's sarcoma. *Am. J. Surg.* 27:7-18, 1935.
12. *Idem*. Diagnosis and treatment of sarcoma of the long bones. *Proc. Internat. Assemb. Inter-State Post Grad. M. A. North America* Atlanta, Georgia, October 15-19, 1928. Pp. 165-182.
13. *Idem*. Some thoughts on the problem of cancer control. *Am. J. Surg.* 14 605-619, 1931.
14. Christian, S. L., and Palmer, L. A. An apparent recovery from multiple sarcoma. *Am. J. Surg.* 4 188-197, 1928.
15. Simmons, C. C. Factors influencing the prognosis. *Surg. Gynec. & Obst.* 69 67-75, 1939.
16. Coley, B. L. Unpublished data.
17. Meyerding, H. W. Ewing's tumor. *Proc. Staff Meet., Mayo Clin.* 14 593-596, 1939.
18. Ewing, J. *Neoplastic Diseases*. Third edition. 1127 pp. Philadelphia: W. B. Saunders Co. 1928.

## MEDICAL PROGRESS

### SYPHILIS

C. GUY LANE, M.D.,\* AND G. MARSHALL CRAWFORD, M.D.†

BOSTON

DURING the past year, there have been so many publications of interest about syphilis that it is again difficult to select material for a progress report. It is of primary interest that the campaign to control syphilis continues unabated and should before long produce noticeable changes in the incidence of the disease. This is especially true in the larger cities, where there is already an apparent drop in syphilis in presumably representative samples of the population.<sup>1</sup> Heretofore, smaller cities and rural communities showed the lowest incidence of syphilis. This reversal seems to indicate that the work has been either less actively pursued in the smaller cities or less effectively promoted. The campaign also has produced numerous publications regarding the effort to prevent venereal disease among the nation's

military forces.<sup>2</sup> Since many army camps are at some distance from towns and cities, the vendors of feminine diversion have taken to wheels. Evidently, prostitution has motorized more rapidly than the army. Regulations have been promulgated, and large restricted areas have been set aside in which trailers and roadside stands are not permitted around certain military posts.

### PUBLIC HEALTH

The first item of note is the recent passage in Massachusetts of a premarital-examination statute. The Massachusetts law<sup>3</sup> differs from most in that there is no provision preventing marriage, regardless of the presence of disease. It is merely required that applicants be examined, and that both parties be informed of the presence of infectious disease and the possibility of transmitting it in marriage and pregnancy. Editorial comment<sup>4</sup> on this statute has been favorable. A similar law has been operating in Virginia for several years, with apparently satisfactory results.<sup>5</sup> It is hoped

Reprints of articles in this series are not available for distribution but the articles will be published in book form. The current volume is *Medical Progress Annual*, 1940 (Springfield, Illinois: Charles C. Thomas Company, 1941) \$4.00.

\*Clinical professor of dermatology, Harvard Medical School, chief, Department of Dermatology, Massachusetts General Hospital.

†Assistant in dermatology, Harvard Medical School, assistant in dermatology, Massachusetts General Hospital.

that this measure will restrain those who should not marry and stimulate them to undergo treatment—perhaps more effectively than if marriage were made illegal. A survey of reports from twenty-six states having premarital laws<sup>6</sup> indicates an incidence of 1.3 per cent positive tests among 677,000 persons. This is lower than the rate for the population as a whole, and should have brought approximately 8800 people under observation. One difficult problem is reciprocity between states having these premarital laws. This matter has already been considered,<sup>7</sup> but the solution is probably somewhat in the future. In one state, a premarital law has apparently reduced congenital syphilis 50 per cent in four years.<sup>8</sup> Marriages were fewer at first, but have been steadily increasing. A particularly good study of the incidence of syphilis by Clarke and his associates<sup>8</sup> was extremely critical of the data previously utilized, and compiled statistics on more than four million people. Each report was reviewed according to rigid criteria, and many groups were discarded, the final analysis being based on about two million cases. The crude rate for the incidence of syphilis was 3.24 per cent on a nationwide basis. Figures for various population groups would cover wide variations. For example, the prevalence of syphilis among the first million selectees and volunteers was 4.52 per cent.<sup>1</sup> This is subject to some possible modification because follow-up studies had not been completed on all positive cases at the time this report was compiled. Statistics should be broken down to cover various sectional groups so that the greatest effort can be directed among the portions of the population that are most heavily infected.

#### SEROLOGIC TESTS

Much effort has been expended on analyzing and improving serologic tests for syphilis. There has perhaps been more confusion in the mind of the profession regarding blood tests than on any other matter relating to this disease. The fourteenth supplement to *Venereal Disease Information*<sup>9</sup> is a monograph devoted to this problem. Every phase of serologic tests for syphilis and their interpretation is thoroughly covered. A review of this work is impossible here, but the supplement can be obtained from the United States Public Health Service for a pittance.

The increasing number of tests for syphilis has led Moore and Eagle<sup>10</sup> to suggest standardization of serologic reports. The more tests one can employ on a given specimen, the greater is the possibility of an accurate result. It is the interpretation of variant reports that is confusing, and the

laboratory director should be the best qualified person to unify conflicting laboratory findings. Thus, these authors recommend that a single report of positive, negative or doubtful be returned from the laboratory, regardless of the type or number of tests employed. This composite report would simplify and clarify the utilization of laboratory data. No information of diagnostic significance would be withheld, since the results of all individual tests should be given on the back of the laboratory slip. A study of the specificity of serologic tests carried out on 40,545 college students of both sexes showed 62 cases (0.15 per cent) that were positive or doubtful,<sup>11</sup> and these data were confirmed by repeat tests. Half these cases failed to exhibit any evidence or history of syphilis. By correlation with the proved cases of syphilis, only 10 cases were considered to have possible false-positive reactions. This incidence (1:4000) of questionable false-positive results seems sufficiently small to justify, as a general public-health measure, the diagnosis of syphilis in clinically normal persons on the basis of repeated positive serologic tests, even in the absence of history or clinical evidence of syphilitic infection.

Moore and Eagle<sup>12</sup> have been investigating quantitative serologic tests for syphilis since 1928, and their report covers 1665 cases. It is essential that these tests be done in series by the same laboratory; otherwise, they are not comparable, and it is emphasized that a single quantitative test is practically useless. Therefore, such procedures are of little value as routine diagnostic measures, nor are they an expression of the severity or gravity of the infection. It has not yet been possible to determine accurately the prognostic value of serial quantitative tests for syphilis in the course of treatment.

It has been conclusively demonstrated that patients with infectious mononucleosis give a positive serologic reaction for syphilis that may persist as long as two months. Publications on this point have been quoted in previous progress reports. It is interesting to note a report of an epidemic of mononucleosis without clinical signs or symptoms.<sup>13</sup> Sixteen out of 108 convalescent rheumatic-fever patients developed mononucleosis during a six-month period. The first case was accidentally discovered during a routine leukocyte count. Blood Wassermann reactions were checked in only 5 cases and were negative in all. This report gives rise to interesting speculation: if infectious mononucleosis exists in an asymptomatic form and if such cases occasionally show positive blood tests, another obscure cause for false-positive serologic tests for syphilis exists. It is unfortunate

that only 5 cases were tested and that only the Wassermann test was employed

Another episode has apparently been proved to provide false-positive serologic reaction for syphilis. Lynch and his associates<sup>14</sup> found that 43 (16 per cent) out of 263 patients exhibited positive tests for two to four months after vaccination for small pox. The same phenomenon was encountered in a study of 20,000 serologic tests for syphilis among Navy personnel after vaccination.<sup>15</sup> Typhoid inoculations did not produce this effect on the serologic tests.

### TRANSFUSION SYPHILIS

The 1940 progress report<sup>10</sup> called attention to the successful use of arsphenaminized citrated blood in the prevention of transfusion syphilis. Further work has been carried out along this line by Eichenlaub and associates,<sup>17</sup> who suggest that 0.01 gm of Mapharsen be added to the sodium citrate solution when blood is withdrawn from the donor. This recommendation is based on a study of 41 cases of transfusion syphilis in which 16 of the donors had syphilis that was not detectable by laboratory methods or physical examinations. The amount of Mapharsen suggested was found to be capable of sterilizing 500 cc of blood known to contain *Treponema pallidum* (rabbit experiments). These authors believe that if the procedure is not accepted as routine, it should at least be used when there is not time to investigate the donor or when any doubt of the absence of syphilis exists. The increase in utilization of blood banks has given rise to another phase of transfusion syphilis. Studies by Turner and Discher<sup>18</sup> and by Bloch<sup>10</sup> are encouraging. Experimental results with citrated blood to which a suspension of virulent *T. pallidum* was added indicate that the infectivity of the treponemes in citrated blood rarely persists for longer than three days at refrigerator temperature. Therefore, there is apparently a definite risk if blood has been preserved for less than seventy-two hours, but not thereafter unless the donor had early syphilis. It is probable that any blood stored for four days or longer can not transmit syphilis.

### CLINICAL PROBLEMS

**Extragenital chancre.** Wilk and Holman<sup>20</sup> reviewed 841 cases of primary syphilis observed over a period of twenty-five years, among which were 68 cases (8.0 per cent) of extragenital chancre. In 39 cases (57.3 per cent), these occurred on the lip. In decreasing order of incidence were lesions on the tonsil, tongue, pharynx, female breast, forehead, chest and anus. Noteworthy cases and the circum-

stances surrounding them were described in detail. The failure of early diagnosis, particularly in unusual locations, was emphasized. Syphilis should always be considered in the face of any persistent lesion with regional lymphadenopathy that does not respond to ordinary therapy.

**Secondary syphilis.** Thomas and Goldstein<sup>21</sup> reported 23 cases of chronic syphilitic tonsillitis, 20 being misdiagnosed before coming to their clinic. The duration varied from two weeks to over three months, and all but one patient showed a secondary eruption. There is nothing characteristic about the appearance of these throats, but they must be differentiated from Vincent's infection and diphtheria. Routine serologic tests for syphilis and a careful examination for other signs established the diagnosis.

**Transmissibility of syphilis.** Pariser<sup>22</sup> studied the infectiousness of vaginal secretions and menstrual blood of 30 untreated syphilitic women by injecting these secretions into rabbits. Vaginal infectiousness was periodically recurrent rather than continuously present, and depended on the presence or absence of lesions. No estimate could be made of the frequency of cervical relapse or of its end point. One infectious relapse occurred six and a half years after the onset of the disease. Physiologic secretions were not infectious in the absence of open lesions.

**Bone and joint syphilis.** Buchman and Lieberman<sup>23</sup> reviewed 89,000 orthopedic cases observed over a period of ten years. Of these patients, 119 (0.13 per cent) had lesions of the bones or joints due to syphilis, 25 were congenital cases, of which 3 exhibited a negative blood reaction, 27 of 84 patients with acquired syphilis showed a negative reaction. The authors attributed this low incidence of bone and joint syphilis to the relative infrequency of lesions of orthopedic importance in the presence of syphilis.

**Cardiovascular syphilis.** Gelperin<sup>24</sup> reported an interesting analysis of 7638 autopsies in which 700 cases (9.1 per cent) with microscopic evidence of syphilitic aortitis were found, excluding developmental complications; he suggests that patients with late latent syphilis, without adequate treatment, be considered as having active syphilitic aortitis. Doubtless, there are dissenters to this opinion. Berk,<sup>25</sup> reporting a clinical and electrocardiographic study of cardiovascular syphilis, believes that the only safe method of diagnosing early syphilitic aortitis with coronary ostial stenosis is with a positive electrocardiogram after a positive exercise test. After the age of fifty, however, he regards this finding as more probably due to coronary sclerosis on a nonsyphilitic basis.

Stewart and Smith<sup>26</sup> found that the administration of potassium iodide causes changes in the electrocardiogram and cardiac rhythm that may be falsely attributed to coronary occlusion. These "toxic manifestations" disappeared after the drug was discontinued.

*Congenital syphilis.* Ingraham et al.<sup>27</sup> have published a comprehensive report on infantile congenital syphilis. It covers a five-year follow-up on 230 children of syphilitic mothers. Re-examination of 70 per cent of the survivors four or five years later revealed no congenital syphilis that had been missed by x-ray and serologic studies during infancy. The mortality among syphilitic infants was 33 per cent, as compared with 10 per cent in the nonsyphilitic group; over three times as many died without therapy as with it, even when inadequately treated. Ingraham believes that hyperpyrexia from intercurrent disease may enhance good results. He also reviews the recent advances in the serologic and roentgenologic diagnosis of infantile congenital syphilis and emphasizes close co-ordination in interpreting blood and roentgenographic changes. Considerable attention is given to titrated serologic studies, and their great value in the early weeks of life is emphasized. Occasionally, a significant change in the titer may not occur until four to eight weeks after the child is born. Sarnat and his collaborators<sup>28</sup> described changes found in the unerupted permanent teeth by roentgenographic study of patients with congenital syphilis; disturbances in development occurred in the neonatal period and earliest infancy. These may be diagnostic when x-ray films of the long bones show nothing, since the teeth changes are permanent, whereas bone lesions are subject to resorption. This is a useful contribution, and one can readily agree with the postulation of the authors that x-ray examination of unerupted teeth should be carried out in conjunction with studies of the long bones. Koons and Kissane<sup>29</sup> studied 100 children with congenital syphilis and 335 others with cardiac disease. No syphilitic heart disease was found, and the authors concluded that syphilis can be practically disregarded as a cause of cardiac disease in children. This bears out a long-accepted corollary. The role of ariboflavinosis in interstitial keratitis has not been entirely clarified. Johnson and Eckardt<sup>30</sup> were unable to produce keratitis in syphilitic rabbits by placing them on a diet deficient in riboflavin. These authors believe that the corneal changes seen with the slit lamp in riboflavin deficiency are not typical of syphilitic keratitis.

*Syphilis and pregnancy.* Peckham<sup>31</sup> studied the effect of syphilis and its treatment on toxemia

of pregnancy in 13,742 consecutive deliveries and found the incidence of toxemia somewhat lower in syphilitic than in nonsyphilitic patients. There was no correlation between the stages of syphilis and frequency of toxemia. The lowest incidence of toxemia was in syphilitic patients treated before, but not during, gestation, the amount of treatment employed being without significance. Half the patients receiving therapy during pregnancy had evidenced toxemia before antisyphilitic treatment was begun. It is obvious from this study that the various degrees of toxemia of pregnancy are entirely unrelated to both syphilis and its therapy.

*Neurosyphilis.* Bottema<sup>32</sup> had the unique opportunity of observing 1470 cases of syphilis in the Dutch Navy that were followed for thirty years. Careful records and very thorough checks on clinical and laboratory findings were available for the entire time. The patients were divided into four groups, as follows: untreated; those receiving mercury therapy only; those given small amounts of arsphenamine; and those receiving intensive arsphenamine therapy. A striking progressive decrease of morbidity in each group left no doubt regarding the value of even small amounts of therapy. This is interesting in view of the theory, maintained by some, that small amounts of the arsphenamines are conducive to the occurrence of neurosyphilis. Alpers and Lesko<sup>33</sup> call attention to the incidence of neurosyphilis with negative cerebrospinal-fluid examinations. Varying percentages of negative fluids are reported for the different types of neurosyphilis, the highest being 23 per cent in vascular neurosyphilis. In many cases of neurosyphilis of all types in which the laboratory reports are negative, clinical symptoms not only remain, but continue to progress. This is especially true of tabes dorsalis and vascular neurosyphilis. Alpers and Lesko conclude that these cases illustrate the tendency to emphasize too strongly the laboratory data to the exclusion of the clinical facts.

*Syphilis and diabetes mellitus.* McDaniel, Marks and Joslin<sup>34</sup> reviewed 15,095 patients with diabetes and found 258 cases (1.7 per cent) of syphilis, 87 per cent of which were latent. In their study, these authors failed to find any "syphilitic diabetes." Not a single case of cure of diabetes was brought about by optimum antisyphilitic therapy. Williams<sup>35</sup> observed that 23 of 1000 patients with severe diabetes and low carbohydrate-tolerance tests, for whom large doses of insulin were required and whose metabolism was difficult to adjust, frequently showed "subpositive" serologic tests for syphilis. Treatment was found to serve

no useful purpose and was often upsetting. He concluded that there was no causal relation between syphilis and diabetes.

*Syphilis and tuberculosis.* The management of syphilis in the tuberculous patient has been discussed by Murphy and Bromberg.<sup>36</sup> Approximately 9 per cent of an adult tuberculous group was found to be syphilitic, which is somewhat higher than the usual figure for this type of patient. These authors confirm the existing belief that syphilis does not materially alter the prognosis of tuberculosis, or vice versa. It was indicated that tuberculous toxemia may occasionally contribute to temporary false positive serologic reactions for syphilis. In hopelessly advanced tuberculosis, any other treatment would be superfluous. Cardiovascular and cerebrospinal syphilis may be debilitating and even fatal in a patient with advanced tuberculosis who otherwise might maintain a satisfactory equilibrium. It is interesting to note a paper by Fujimori<sup>37</sup> concerning the influence of syphilis on the resisting power of a living organism. It was found that experimental syphilitic infection decreased resistance and rendered the animals more susceptible to other infections.

#### THErapy

*Early syphilis.* An outstanding study on the treatment of syphilis has been that of Padget.<sup>38</sup> A very difficult problem in evaluating treatment, especially new drugs and new methods, has been the lack of necessary long-term statistics to show the end results. In a disease that is so chronic, insidious and prone to relapse, the first results of treatment are of value only for prognosis of the immediate future. It is a long-term follow-up of therapeutic results in early syphilis by modern methods that Padget has been able to present for the first time. Five hundred and fifty-one patients were completely re-examined five or more years after the termination of treatment "Cure," as defined by Padget, consisted either in reinfection or in freedom from symptoms, negative physical examination, repeatedly negative serologic reactions for syphilis, normal cerebrospinal fluid and normal roentgenograms of the cardiovascular stripe. In the light of these criteria, only slightly less than two thirds of these cases achieved cure, the mean period of observation being about eleven years. Two hundred and sixty-eight patients were examined after five years had elapsed and, again, at the end of ten years. No case showed a less satisfactory result at the end of ten years than after only five years. This is perhaps one of the most significant features of the study and indicates that, in a patient with early syphilis ade-

quately treated by modern methods who maintains such a "cure" for five years, the possibility of further trouble is extremely remote. Padget's other findings in the study of this group are confirmative of the accepted opinions regarding race, sex, stage of disease at onset of treatment and so forth. The final results were found to be dependent on both the type and the amount of treatment, the alternating continuous system of therapy being clearly superior to other programs. It was emphasized that the continuity must be absolute, especially in the first six to twelve months; 90.4 per cent of patients who had unbroken treatment for the first year were cured, which was the highest figure. The worst results were obtained in the seropositive primary cases, in only 55 per cent of which cure was achieved, neurosyphilis being more than twice as common in this group as any other. Padget's paper is of considerable value in that it has at last provided the absolute proof of several cardinal principles in the treatment of syphilis as emphasized by the modern school of syphilologists. In the light of this, a review by Cole<sup>39</sup> is very timely: it gives an excellent survey of the problems of the general practitioner in the treatment of syphilis and provides cogent answers.

*Bismuth compounds.* It is only in approximately the last twenty years that bismuth has been used in the treatment of syphilis. Walsh and Becker,<sup>40</sup> who have reviewed the status of this drug, emphasize the fact that it cannot be relied on as the sole antisyphilitic drug to the exclusion of the arsphenamines. According to these authors, the present consensus seems to be that bismuth salicylate in oil is the most suitable from the standpoint of therapeutic effect, low toxicity and prolonged action. A plan of treatment that includes the advocacy of a much larger number of bismuth injections than is usually employed, especially in neurosyphilis, is outlined, but their report indicates slightly better results. Considerable experimental work with oral bismuth administration in animals suggests its effectiveness in early syphilis. A recent paper by Hanzlik and Van Winkle<sup>41</sup> is confirmatory. Lambert,<sup>42</sup> however, shows that oral bismuth is not suitable for the treatment of early syphilis in the human organism. Six seronegative cases of primary syphilis and 2 in the secondary stage were treated with Sobisminol, six to nine capsules daily, for a period of nearly four months each. Five of the seronegative primary cases developed a positive blood Wassermann, and 4 of these 5 developed a clinical secondary stage despite the above therapy. The implication is obvious.

*Arsenical therapy.* Stokes and Beerman<sup>43</sup> reviewed the use of trivalent arsenicals in syphilis

from the standpoint of recent advances, comparisons and evaluations. It is a very comprehensive study including a discussion of nine different drugs, methods of testing, new technics, the "five-day plan," the laboratory value of drugs compared with their usefulness to the practicing physician, to the expert and to the demands of the public-health officer. This paper is certainly worth reading in the full text by those who aspire to any degree of familiarity with these drugs. It is brought out that although Mapharsen is apparently the best drug in many respects, there is as yet insufficient study of infectious relapse following its use. The value of Bismarsen in childhood and in cardiovascular syphilis is stressed. In the end, however, the authors consider arsphenamine the most effective drug in everything except central-nervous-system syphilis.

*Interstitial keratitis.* Klauder and Vandoren<sup>44</sup> presented an excellent report on 532 cases of interstitial keratitis, with particular reference to treatment. All the cases, which were pooled from five institutions, were treated or observed for at least one year. The median age at onset was twelve years in females and thirteen years in males. The two commonest stigmas present in conjunction with the keratitis were Hutchinsonian teeth (40 per cent) and bone and joint lesions (35 per cent). It was interesting that 42 per cent of the cases were bilateral within a month of onset, and that 71 per cent became bilateral within two years. The figure then crept very slowly to 79 per cent at the end of ten years. The fact that hyperpyrexia (malaria or hyperthermia) should be instituted at once was emphasized. Immediately following this, at least twenty intravenous arsenical injections were advocated, in conjunction with bismuth. This combined treatment should be started between the fever treatments if malaria therapy is not used, and the first few injections of bismuth should be the water-soluble form. In the prevention of relapse, chemotherapy combined with fever treatments was clearly superior — less than 0.5 per cent as compared with 13 to 18 per cent by other methods. It is imperative that treatment be continuous during the active stage to achieve the best percentage of good results, yet in the end there was 10 to 12 per cent of blindness from all methods. Apparently a tenth of the patients will be blind regardless of treatment. It was brought out that treatment during the inactive stage was of limited value in improving the final vision, but it should be noted that Klauder and Vandoren do not mean treatment to be dispensed with, since the patient still has congenital syphilis. It was stated that iodides have an unfavorable influence on the final

vision. In considering this paper, one should remember that all the work was done before the introduction of riboflavin. Cole<sup>39</sup> is now of the opinion that the combination of hyperpyrexia and large doses of riboflavin (vitamin B<sub>2</sub>) is the method of choice in the treatment of interstitial keratitis. He believes that other treatment should be withheld until the fever is terminated.

*Central-nervous-system syphilis.* Spiegel, Leifer and Sarason<sup>45</sup> have reported on the use of a new drug, Aldarsone, in neurosyphilis. This study extends over a period of five years and covers 133 patients with various types of the disease. Many of the patients received courses of bismuth injections concurrently, and fever therapy was given when indicated. The drug was well tolerated by the majority of patients, and no very serious reaction occurred. The results seem to indicate that Aldarsone is effective in neurosyphilis, and that optic atrophy is apparently no contraindication to the employment of this drug. This is encouraging, and if further work and longer periods of observation bear out these results, it will be a definite step in advance. Epstein and Solomon<sup>46</sup> stated that there are three factors relating to the mechanism of artificial fever: destruction of treponemes by elevation of body temperature, biologic response to nonspecific foreign protein, and alterations produced in the brain parenchyma by the malarial organism. If one grants these three factors, one is still somewhat at a loss to assess their relative importance. Epstein and Solomon have considered fever therapy in general and its effect on the various forms of neurosyphilis. The main point is their plea for the use of fever therapy in the treatment of asymptomatic neurosyphilis, since "accumulated clinical evidence indicates that fever therapy adequately prevents clinical neurosyphilis." This statement is made with the reservation that fever therapy is not so effective in juvenile paresis. A five-year comparison of artificial fever and therapeutic malaria was reported by Ewalt and Ebaugh.<sup>47</sup> Two hundred and thirty-two cases were equally divided without selection. All the malaria cases and 66 per cent of the artificial-fever patients were followed for five years (or until death). Remission or improvement occurred in 69 per cent of the fever group and in 58 per cent of the malaria group. It must be stated that the former underwent consistently higher temperatures. The authors raise the possibility that these higher temperatures are responsible for better results and suggest that the better physical condition of the fever patients at the end of treatment may be significant. Malarial therapy and artificial fever are not available in many institutions, however,

and several other methods of producing fever have been suggested. Kulchar and Card<sup>48</sup> report the use of typhoid "H antigen" vaccine, which eliminates the objectionable features of the old vaccine. One hundred and eighteen cases of various types of neurosyphilis were treated, and 94 were followed for periods of four to forty-six months. Most of these patients had previously had some chemotherapy. The symptomatic and serologic improvement compared favorably with the results of other forms of fever treatment. Kulchar and Card believe that the present method has a number of advantages in that fever can be produced, carefully controlled, and terminated as desired. It is stated that the relatively slight amount of constitutional reaction accompanying the fever makes it applicable with safety to many patients unable to receive other forms of fever treatment.

**Massive-dose therapy.** Reference has been made to this subject in previous progress reports, with emphasis on the fact that, although promising, the procedure must continue to be an experimental method for some time and should be used only in hospitalized cases under close observation, limited to cases of early syphilis, and employed only in well-equipped universities and syphilis centers. This opinion is echoed by Shaffer,<sup>49</sup> who calls attention to the fact that the method is now being tried in eight states under the supervision of the United States Public Health Service.<sup>50</sup> The instigators<sup>51</sup> of this procedure have continued its use with the substitution of Mapharsen for neoarsphenamine. Three hundred and eighty-two cases have been treated in all (neoarsphenamine and Mapharsen). There were significantly fewer reactions in the Mapharsen series. Including 15 re-treated cases, satisfactory results were attained in all respects in 88 per cent of the patients. There was 1 death, and 1 case showed a positive cerebrospinal fluid. There were 5 per cent of irreversible failures, but this figure might have been reduced if re-treatment had been attempted throughout. A committee representing the original group and the United States Public Health Service<sup>52</sup> evaluated all available data of the work so far accomplished. It includes thirteen large hospital clinics in nine cities. All the work reported was done with Mapharsen, and nearly all the serologic study was carried out in one of two laboratories. Nine hundred and sixty-eight cases of early syphilis were treated. Both sexes were included, but no pregnant women were treated. The results were satisfactory in 85 per cent of the cases. Toxicologic manifestations were comparatively mild. Adding these to all cases reported

in the literature from all sources, there have been 5 deaths (0.3 per cent) in 1600 patients. Apparently, the continuance of this study in well-organized centers is warranted. In the discussion of this paper, several authorities warned against release of the technic for general use. Cole<sup>53</sup> advocated conservatism and stated that he knew of several as yet unreported deaths. In his opinion, this treatment is still very much in the experimental phase. Elliott,<sup>52</sup> in closing the discussion, stated that some similar form of therapy may evolve to provide better results (and, it is hoped, fewer untoward results) than the treatment schedule in use at present. A modification of the massive-therapy program has already been reported by Schoch and Alexander,<sup>54</sup> who employed a multiple-dose, syringe-technic treatment schedule that utilizes injections twice a day. The series is small and the time of study is short, but all things must have a beginning, and Schoch is possibly on the right track.

## REFERENCES

1. Vonderlehr R. A., and Huston J. L. Syphilis among selectees and volunteers: prevalence in first million men examined under the selective service act of 1940. *J. A. M. A.* 117:1350, 1941.
2. Hitchens A. P. How the Army protects soldiers from syphilis and gonorrhea. *J. Social Hyg.* 27:103, 1941.
3. Anthony R. H. The defense program to date: an appraisal. *Bull. Mass. Society Soc. Hyg.* 11 No. 3 p. 3, 1941.
4. Moore J. E. Venereal diseases and national defense. *J. A. M. A.* 117:255, 1941.
5. An Act further regulating the filing of notices of intention of marriage, and the delivery of certificates of such intention and the return of unused certificates. Commonwealth of Massachusetts Gen. Laws, Chap. 601, 1941.
6. Editorial. Premarital medical examinations. *New Eng. J. Med.* 225:344, 1941.
7. Edwards M. S. Premarital examination laws in operation. *J. Social Hyg.* 26:217, 1941.
8. Shippey W. M. The evaluation of premarital legislation. *J. A. M. A.* 116:2006, 1941.
9. Conference of state and territorial health officers. V. Reciprocity between states in premarital examinations to detect syphilis. *Ven. Dis. Inform.* 22:236, 1941.
10. Clarke, C. W. di Mario M., and Edwards M. S. How many people have syphilis? A brief report on prevalence of syphilis in the United States. *J. Social Hyg.* 27:269, 1941.
11. Hinrichsen J. *Modern Serologic Tests for Syphilis and Their Interpretation by the Physician.* Venereal Disease Information. Supp. No. 14. 81 pp. Washington: Government Printing Office, 1941.
12. Moore J. E., and Eagle H. The confusing multiplicity of serologic tests for syphilis: standardization of the serologic report as a possible solution. *J. A. M. A.* 117:243, 1941.
13. Eagle H. On the specificity of serologic tests for syphilis as determined by 40,545 tests in a college student population. *Am. J. Syph., Gonorr. & Ven. Dis.* 25:7, 1941.
14. Moore J. E., and Eagle H. The quantitative serologic test for syphilis: its variability, usefulness in routine diagnosis, and possible significance: a study of 1665 cases. *Ann. Int. Med.* 14:1802, 1941.
15. Rejersbach G., and Lenert, T. F. Infectious mononucleosis without clinical signs or symptoms. *Am. J. Dis. Child.* 61:237, 1941.
16. Lynch, F. W., Boynton, R. C., and Kimball A. C. False positive serologic reactions for syphilis due to smallpox vaccinations (vaccinia). *J. A. M. A.* 117:591, 1941.
17. Thomas, G. E., and Garrity, R. W. Routine Kahn blood reactions report of 10,000 tests made on naval recruits. *U. S. Nav. M. Bull.* 39:274, 1941.
18. Routine Kahn blood reactions: supplementary report of 20,000 tests made on naval recruits with observations on the relationship of convalescent vaccination to the false positive test. *U. S. Nav. M. Bull.* 39:272, 1941.
19. Lane, C. G., and Crawford G. M. Syphilis. *New Eng. J. Med.* 222:224, 1940.
20. Eichenlaub, F. J., Stolar, R., and Wade, A. Prevention of transfusion syphilis. *Arch. Derm. & Syph.* 44:441-445, 1941.
21. Turner, T. B., and Diecker, T. H. Duration of infectivity of *Treponema pallidum* in citrated blood stored under conditions obtaining in blood banks. *Bull. Johns Hopkins Hosp.* 68:269, 1941.
22. Bloch, O., Jr. Loss of virulence of *Treponema pallidum* in citrated blood at 5°C. *Bull. Johns Hopkins Hosp.* 68:412, 1941.
23. Wile U. J., and Holman, H. H. A survey of sixty-eight cases of extra genital chancres. *Am. J. Syph., Gonorr. & Ven. Dis.* 25:58-66, 1941.



- 21 Thomas, E. W., and Goldstein, D. H. Chronic tonsillitis in secondary syphilis—differential diagnosis from diphtheria and Vincent's infection. *New York State J. Med.* 41:256-259, 1941
- 22 Pariser, H. Studies of the transmissibility of syphilis the infectiousness of the vaginal secretions and menstrual blood of syphilitic women. *Am. J. Syph., Gonorr. & Ven. Dis.* 25:339-374, 1941
- 23 Buchman, J., and Lieberman, H. S. Prevalence of syphilis of the bones and joints report of a statistical study at the Hospital for Joint Diseases, with a review of the literature. *Arch. Dermat. & Syph.* 44:1-12, 1941.
- 24 Gelperin, A. The incidence of syphilitic aortitis in a representative municipal hospital. *Am. Heart J.* 20:340-344, 1940
- 25 Berk, L. H. Cardiovascular syphilis a clinical and electrocardiographic study. *New York State J. Med.* 41:223-233, 1941.
- 26 Stewart, H. J., and Smith, J. J. Changes in the electrocardiogram and in the cardiac rhythm during the therapeutic use of potassium salts. *Am. J. M. Sc.* 201:177-197, 1941
- 27 Ingraham, N. R., Jr., Shaffer, B., Spence, B. E., and Gordon, J. H. The adequate diagnosis of infantile congenital syphilis. *Arch. Dermat. & Syph.* 43:323-340, 1941
- 28 Sarnat, B. G., Schour, I., and Heupel, R. Roentgenographic diagnosis of congenital syphilis in unerupted permanent teeth. *J. A. M. A.* 116:2745-2747, 1941
- 29 Koons, R. A., and Kissane, R. W. The incidence of heart disease in children with congenital syphilis. *Urol. & Cutan. Rev.* 44:673, 1940
- 30 Johnson, L. V., and Eckardt, R. E. Ocular conditions associated with clinical riboflavin deficiency. *Arch. Ophth.* 24:1001-1005, 1940
- 31 Peckham, C. H. The effect of syphilis and its treatment on the incidence of toxemia of pregnancy. *Am. J. Syph., Gonorr. & Ven. Dis.* 25:280-285, 1941.
- 32 Bottema, C. W. The incidence of neurosyphilis, especially parasyphilis. *Nederl. tijdschr. v. geneesk.* 84:4272-4276, 1940
- 33 Alpers, B. J., and Lesko, J. M. Neurosyphilis with negative spinal fluid. *Urol. & Cutan. Rev.* 42:225-229, 1941
- 34 McDaniel, L. T., Marks, H. H., and Joslin, E. P. Diabetes mellitus and syphilis a study of two hundred and fifty eight cases. *Arch. Int. Med.* 66:1011-1051, 1940
- 35 Williams, J. R. Syphilis and diabetes mellitus a critical study of their relation to each other in 1,000 cases of diabetes mellitus. *New York State J. Med.* 41:252-255, 1941.
- 36 Murphy, P., and Bromberg, L. Management of syphilis in the tuberculous patient. *Am. Rev. Tuberc.* 43:748-760, 1941.
- 37 Fujimori, M. The influence of syphilis on the resisting power of a living organism. *Jap. J. Exper. Med.* 18:117-129, 1940
- 38 Padgett, P. Long-term results in the treatment of early syphilis. *Am. J. Syph., Gonorr. & Ven. Dis.* 24:692-731, 1940. Long-term results in the treatment of early syphilis. *J. A. M. A.* 116:7-11, 1941.
- 39 Cole, H. N. Syphilotherapy recent advances. *J. A. M. A.* 117:1091-1095, 1941.
- 40 Walsh, E. N., and Becker, S. W. The use of bismuth compounds in syphilotherapy. *J. A. M. A.* 116:484-489, 1941.
- 41 Hanzlik, P. J., and Van Winkle, W., Jr. Effects of sobisminol solution orally in experimental syphilis. *Am. J. Syph., Gonorr. & Ven. Dis.* 25:508-510, 1941.
- 42 Lambert, A. Peroral bismuth as initial therapy in syphilis. *Union méd. du Canada* 70:502, 1941
- 43 Stokes, J. H., and Beerman, H. The trivalent arsenicals in syphilis some recent advances, comparisons and evaluations. *Am. J. M. Sc.* 201:611-625, 1941.
- 44 Klunder, J. V., and Vandoren, E. Analysis of 532 cases of interstitial keratitis with particular reference to standardization of treatment. *Ven. Dis. Inform.* 22:307-322, 1941
- 45 Spiegel, L., Leifer, W., and Sarason, H. Treatment of neurosyphilis with a new pentavalent arsenical, aldarson. *Am. J. Syph., Gonorr. & Ven. Dis.* 25:472-485, 1941
- 46 Epstein, S. H., and Solomon, H. C. Fever therapy in diseases of the nervous system. *M. Clin. North America* 24:1555-1572, 1940
- 47 Ewalt, J. R., and Ebaugh, F. G. Treatment of dementia paralytica a five-year comparative study of artificial fever therapy and therapeutic malaria in two hundred and thirty-two cases. *J. A. M. A.* 116:2474-2477, 1941.
- 48 Kulchár, G. V., and Card, J. F. Divided doses of typhoid H antigen vaccine in the treatment of syphilis. *Am. J. Syph., Gonorr. & Ven. Dis.* 25:466-471, 1941.
- 49 Shaffer, L. W. Massive arsenotherapy in early syphilis. *J. Michigan M. Soc.* 40:529-531, 1941.
- 50 Rattner, H. Intensive treatment of early syphilis. *Illinois Health Messenger* 13:44-47, 1941
- 51 Leifer, W., Chargin, L., and Hyman, H. T. Massive dose arsenotherapy of early syphilis by intravenous drip method recapitulation of the data (1933 to 1941). *J. A. M. A.* 117:1154-1160, 1941.
- 52 Elliott, D. C., Bachr, G., Shaffer, L. W., Usher, G. S., and Lough, S. A. An evaluation of the massive dose therapy of early syphilis. *J. A. M. A.* 117:1160-1166, 1941.
- 53 Cole, H. N. Discussion of Elliott et al.<sup>52</sup>
- 54 Schoch, A., and Alexander, L. J. Short term intensive arsenotherapy of early syphilis, preliminary report. *Am. J. Syph., Gonorr. & Ven. Dis.* 25:607-609, 1941.

**CASE RECORDS OF THE  
MASSACHUSETTS GENERAL HOSPITAL**ANTE-MORTEM AND POST-MORTEM RECORDS AS USED  
IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

---

CASE 28031

## PRESENTATION OF CASE

A thirty-nine-year-old linotype operator was admitted to the hospital because of disorientation and various motor weaknesses following a complicated illness.

He was in good health until seven months before entry, when he had a "cold," associated with generalized aches and pains. This was followed by a brief spell of intense pain in the left lower quadrant of the abdomen, with radiation to the lumbar region. There were no associated urinary symptoms. The temperature was not noted. At the same time, there was gradual onset of constipation; this was significant because the patient had always had very regular bowels. After a month, he had another "cold," accompanied by generalized malaise and pain in the left lower quadrant, radiating to the lower left side and back. His physician, who reported a urinalysis as negative, diagnosed "kidney stone" and gave no treatment. In the next two or three months, the patient noted increasing nervousness and restlessness, particularly at night. He had to stop work because of intense, persistent pain in the back. He lost appetite and began to lose weight, dropping about 50 pounds in the period before entry. Two months before admission here, he entered a New York City hospital, where he was told that he had pus in the urine and, following cystoscopy, that "an abscess of the left kidney was drained." After the cystoscopy, he passed clots of blood in the urine. The bladder was washed out several times. After the patient left the other hospital, the pain in the back still persisted. He felt "warm" on several occasions; however, it is not known whether he had actual fever. At about this time, he became quite "nervous and jittery." A local physician gave him some sort of sedation, as well as light and diathermy treatment to the back, and a calcium preparation intravenously. About four weeks before entry, vision became hazy, and it was noted that there was occasional lateral deviation of the right eye. The patient began to complain of pain in both ears and of throbbing, generalized headaches. He became increasingly slow in his reactions, and seemed

somewhat dazed, although rational. The left leg appeared to drag slightly when he walked. It is not known whether the leg was weak or whether he simply favored the leg because of pain in the left side of the back. Three weeks before entry, he motored some two hundred miles to Boston, thinking that the change in surroundings might benefit his nervousness. A few days after he arrived in Boston, a physician who was called because of excruciating back pain told the family that the liver was enlarged and the blood pressure normal. At night, twelve days before entry, the patient was suddenly found to be breathing stertorously. The mouth was pulled to the right side, there was paralysis of the left arm, and he could not speak. The next day, he was taken to another physician, who found that the left arm and left side of the face were paralyzed, and that the patient was unable to speak clearly. The blood pressure was 170 systolic, 90 diastolic. The patient then entered another hospital. After several days, there was some improvement in speech, but he remained disoriented. A lumbar puncture at this time showed that the pressure, cell count and protein were within normal limits; the Wassermann and gold-sol reactions were negative. A roentgenogram of the skull was negative. Three days before entry here, neurologic examination showed the patient to be disoriented, with a left central facial paralysis, left-sided weakness of the tongue, paralysis of the left vocal cord, weakness of the right arm and leg, and a questionable right Babinski plantar response. He was transferred to another hospital, with a diagnosis of thrombosis of the posterior inferior cerebellar artery. On arrival at that hospital, a small amount of bleeding from an old perforation of the left eardrum was noted. Physical examination was negative, except for the findings of a moderately soft, movable lymph node, measuring about 3 by 1.5 cm. in the right axilla, and a sharp, irregular, palpable liver margin. The blood pressure was 194 systolic, 104 diastolic. The temperature was 98°F. Neurologic examination was essentially as noted in the other outside hospital, with the addition of a possible right hemianopsia. Examination of the blood showed a red-cell count of 4,620,000 with 81 per cent hemoglobin, and a white-cell count of 18,450 with 68 per cent polymorphonuclears and 16 per cent band forms. The nonprotein nitrogen was 38 mg. and the serum bromide 6 mg. per 100 cc. The sedimentation rate was 32 mm. in two hours. A spinal tap gave clear fluid under an initial pressure of 120 mm. of water. There was good response to compression of the right jugular vein, but no response to

compression of the left. The fluid showed one polymorphonuclear and four red cells per cubic millimeter. The protein was 34 mg. per 100 cc. The Pandy, gold-sol, Hinton and Wassermann reactions were negative. Roentgenograms of the lumbar spine and of the skull, including special mastoid films, were all negative. Two days later, the temperature was 100.8°F. rectally and appeared to be rising. The patient was transferred to this hospital for possible surgical intervention.

The family and the remote past histories were irrelevant, except that the patient had had "ear trouble" in infancy, and had had chronic drainage from his left ear on many occasions in childhood and in later life.

On admission to the hospital, the patient was somewhat emaciated and delirious; he thrashed about in bed and talked incoherently. There were several, apparently self-inflicted, abrasions on the left foot, and the nail of the right great toe appeared recently avulsed. There were forced movements of the eyes to both sides, more especially to the left. There was suggestive left facial paralysis. The right arm and leg were less active than the left, but were no longer paralyzed. The reflexes were essentially normal. The fundi did not seem abnormal. The heart was not enlarged, and the sounds were of good quality, without murmurs. The aortic second sound was louder than the pulmonic second sound. The liver edge was sharp and firm, one fingerbreadth below the costal margin.

The temperature was 101.5°F., the pulse 132, and the respirations 20. The blood pressure was 175 systolic, 85 diastolic.

Examination of the blood showed a red-cell count of 4,450,000 with 80 per cent hemoglobin, and a white-cell count of 22,750 with 82 per cent polymorphonuclears. The nonprotein nitrogen was 24 mg., the serum albumin 5.4 gm. and the serum globulin 2.1 gm. per 100 cc. The carbon dioxide combining power was 27 vol. per cent, and the chlorides 95.3 milliequiv. per liter. The bromide level was 0.

On the second hospital day, a few brownish petechial spots were noted on the skin of the abdomen. These had not been present when the patient was examined in the outside hospital from which he had been last transferred. The questionable left facial paralysis had cleared. Paralysis of the right arm gradually appeared. The plantar responses were equivocal. On the third hospital day, the temperature rose sharply to 106°F. The patient became quite cyanotic and breathed with apparent difficulty. Dullness was noted in the right infraclavicular region, with palpable rhonchi.

There were scattered loud bronchial breath sounds and coarse and fine rales. A blood culture was taken, and sulfadiazine was started. Death supervened.

#### DIFFERENTIAL DIAGNOSIS

DR. WILLIAM DOCK\*: The occupation was probably not related to the rest of the story. I do not know what illnesses the operators of linotype machines have. On admission, the patient was disorientated, and I dare say his friends gave the complaint, which turns out to have been incorrect, for hazy vision a month earlier means that motor weakness for more than twelve days concluded an illness of seven months. He had a "cold," but we do not know what that means. The intense pain in the left lower quadrant may have been due to a renal stone, or to a diverticulitis. About this time, the patient was constipated; that does not mean anything localized in the large bowel, for with any sort of illness, episodes of constipation and anorexia are likely to occur. He had another "cold,"—I take it to be a febrile illness each time,—with chilly sensations and aching. Nothing is said about sneezing and running nose, and probably it was not an upper respiratory infection or cold in the ordinary sense.

The pain recurred and again was severe, and from this point on his personality went to pieces, with nervousness and restlessness, and he stopped work because of intense pain in the back. He lost appetite and 50 pounds of weight in the following month. The pain may have been renal colic; it may have been due to retroperitoneal tumor, involving the nerve roots, but remission in such cases is rare. It may have been due to disease in the vascular bed behind the peritoneum, a mycotic aneurysm or some other vascular lesion. I remember one case of brucellosis in which the presenting complaint was severe backache, which was due to mycotic aneurysm.

Now the story becomes murky. After cystoscopy, the patient passed blood clots in the urine. The examiners may have opened up a perinephritic abscess with the urethral catheter, and may actually have encountered an abscess in one of the pyramids and removed pus, but that sounds improbable. After that, there was some washing out of the bladder, but the pain in the back was unaffected. I do not believe, then, that the pain in the back was related to the alleged kidney abscess.

The personality became worse and worse, and the patient was hard to live with. When put on

\*Professor of pathology, Cornell University Medical College, New York City.

sedative treatment and intravenous therapy, he developed motor weakness for the first time: the vision became hazy, and he had lateral deviation of the right eye. I assume that he had diplopia and wonder if he had intracranial disease—either a vascular lesion, tumor or abscess.

The patient had severe pain in both ears and headache, so that we think more of tumor than of vascular disease. He became slow in his reactions, was somewhat dazed, and had trouble with the left leg. The deviation of the right eye makes us think of a left-sided lesion in the temporal region, whereas the trouble in the left leg should have come from a lesion on the other side.

Even the trip to Boston does not seem to have relieved the symptoms. The pain grew worse, the liver was found to be enlarged, and the blood pressure was normal at this time. The liver makes us think of tumor, with metastases. The patient was found with stertorous breathing, and had palsy on the left side, including the face and the left arm. The blood pressure was higher—the blood pressure may be elevated by intracranial tumor or intracranial disease acting as tumor. Soon, the patient seemed better, but was still disorientated. Lumbar puncture was negative.

Now we get into more trouble. There was left facial paralysis, with weakness of the right arm and leg, so that we must put the lesion below the tentorium to give a crossed palsy.

The patient entered this hospital, where he remained, and we have a series of examinations—all done by the same people, apparently. Here for the first time is noted evidence of an old otitis media, which makes us think more of abscess than of tumor. A movable lymph node in the right axilla was found; this may or may not have had anything to do with the case. At this time, the liver was sharp and irregular. If it was irregular, the patient must have had cirrhosis or tumor, but the observation may not have been correct. The blood pressure was still high, which makes us think of vascular disease. The sudden onset of hypertension with this sort of story is characteristic of diseases like periarteritis nodosa. But, so far, there is nothing else to go with it. The temperature was only 98°F. There was a possible right hemianopsia. How one can tell about that with any degree of accuracy in a disorientated patient, I do not know. Perhaps, on that day, he was not so disorientated. He had rather marked leukocytosis, with normal blood nonprotein nitrogen, and his troubles were not due to bromidism, with only 6 mg. per 100 cc. in the blood, which is very low. These neurologic findings certainly cannot be accounted for by sedation. The high leukocytosis and the sedimentation rate suggest

tumor, with much necrosis or infectious disease, such as abscess or periarteritis.

We come to the most striking thing in the history, for, if correct, it gives definite localization of the lesion. There was good response to compression of the right jugular vein but no response on the left. If that observation is correct, we can build up a whole diagnosis on it. However, it may be a historical landmark; he might have had lateral-sinus thrombosis early in life and been left with this. On the other hand, it may explain the whole business. The two bouts of "cold" might have been exacerbations of petrositis, with a jugular thrombophlebitis, followed by some sort of embolic lesion occupying the temporal fossa on the left side. If the patient had petrositis, he apparently had no meningitis with it. The spinal-fluid protein content was low, and the roentgenograms, including the special mastoid films, were negative. If that rules out petrositis as well as mastoid disease, I do not know what to do with the old otitis media and apparent obstruction of the jugular vein on the same side.

At last, the temperature began to rise. If the patient had periarteritis all this time, I think he should have had fever on previous occasions; but that is not necessarily so. The ear trouble is stated to date back to infancy, and he had had trouble of that sort off and on all his life. It may be that he had petrositis and extension of inflammation to the jugular bulb without any marked bone destruction, but it is not a helpful thing that the one syndrome that would be diagnostic—the Gradenigo syndrome (facial pain and sixth-nerve palsy due to petrositis)—is missing. The only sign of eye trouble was presumably the third nerve on the opposite side—nothing very helpful there.

When he came into the hospital, the patient still had left facial paralysis, and the right arm and leg were paralyzed and weak. The fundi were not abnormal, which certainly means that there was no malignant hypertension. It does not rule out periarteritis nodosa, however. The heart was not enlarged. There were no abnormal findings except that the liver edge was sharp and firm one fingerbreadth below the costal margin. If he had had chronic suppurative disease for years, he might have amyloid.

We then have some assorted findings: the temperature was higher, the blood pressure was still high, and the patient had marked leukocytosis but a normal blood nitrogen. The carbon dioxide combining power and the chloride values were a little on the low side, which will not help our diagnosis, and there was no bromide in the blood.

What astonishes me is that on this man, who had intracranial complications of some sort, no

chest plate was taken. The first thing we think of with a man with something in his head is to rule out bronchiogenic carcinoma.

DR. GEORGE W. HOLMES: We have a chest plate, which does not seem to have been reported. The interesting thing is this increase in the supracardiac shadow. The shadow has a very sharply defined margin and apparently extends under the clavicle, but I do not believe it reaches the apex. It seems to me that there is a lesion extending from the sternal notch to the region of the lung root. There is no evidence of disease of any kind in the lungs.

DR. DOCK: Do you think it could be a sulcus tumor?

DR. HOLMES: It could be, but I doubt it; there is not enough in the apex. It apparently does not extend into the pleura. It may extend across the mediastinum. It has the somewhat caplike shadow that one sometimes sees in certain tumors of the mediastinum. There is no enlargement of the heart shadow, and the heart looks perfectly normal in shape. The aortic knob is probably normal, and there is no erosion of the ribs, so that I do not believe that there is congenital anomaly of the heart or great vessels. So far as I can tell from this plate, which did not have quite enough exposure, there is no compression of the trachea or of the bronchi. A mass of lymph nodes in that region might look like this, but the shadow is smooth on the outside border, not lobular as a shadow due to glands would be. In addition, there is a high diaphragm on the right side, and the liver appears large.

We have pretty good evidence that the petrous tip is normal—no tumor in the internal auditory canal, and a normal mastoid region. It is rather unusual to have disease of the petrous tips without disease of the mastoid process. All the evidence we have in the skull is quite convincingly negative.

DR. DOCK: One other thing surprises me: we have all these milliequivalent levels in the blood, but there is no report of urine examination. The only reason I am interested in the urine at the moment is that if the patient had periarteritis or if the liver enlargement were due to amyloid, he might have had protein in the urine. I do not know what to do with the shadow in the mediastinum. I am sorry I asked for that chest plate.

DR. CHARLES DERRICK: The urine was not recorded because the patient was incontinent.

DR. DOCK: Then we shall not know about that. Perhaps it is not important.

When we talk about diseases that begin in the lower quadrants, causing pain and enlarged livers,

mediastinal shadows and intracranial lesions, we think among other things of a tumor beginning in the testis. I should like to know whether this patient had testes in the scrotum. He had been to a urologist and five physicians—I suppose that is known.

DR. TRACY B. MALLORY: The testes were in normal position.

DR. DOCK: Tumor beginning in an undescended testis sometimes gives pain in the belly, frequently metastasizes to the brain, and there causes very rapid changes of psyche and motor signs, not lasting over months, but a few days as innumerable intracranial metastases begin to go to pieces; but here there is no evidence of that type of tumor.

We come back to this man, who was rapidly deteriorating mentally, who had had numerous other signs of cerebral involvement, most of which cleared up, but whose paralysis of the right arm proved lasting and who died with a high temperature, 106°F. It seems high for any sort of sepsis and suggests that the intracranial lesion might have encroached on the hypothalamic region. My guess in this case, before knowing about the chest x-ray films, was based on the assumption that he had some disease of the left jugular vein. If we accept that (and I must admit that it is a gamble), the case was one of chronic otitis media, without much damage in the mastoid or petrous bone, but with extension of inflammatory disease to the jugular bulb and, finally, brain abscess. The lesion in the belly that caused the pain, whatever it should turn out to be, and these things in the brain may all be hematogenous metastases or suppuration due to organisms of very low virulence that had entered from the otitis media. Thus, I should guess chronic brain abscess, presumably in the temporal lobe, which seems the most likely region for this process. I do not know whether to put it on the right or left, but because the patient had more disease on the left we might put it there. He may have had terminal septicemia or meningitis.

But the chest x-ray film shows the liver to be so enlarged that it makes us think of tumor, and in the end all this nicely built-up story will go to pieces and we shall find that tumor, with a good deal of necrosis, caused the trouble. This would explain the shadow in the mediastinum: that is, tumor in the mediastinum, tumor in the liver and retroperitoneal tissues and intracranial metastases. I do not know how else to account for the enlarged liver. It seems incredible that the patient would have so many abscesses in the liver as the result of septicemia, and I am therefore hesitant

to account for the huge liver on that basis. The mediastinal shadow could also be accounted for by sepsis. Perhaps he also had a suppurative lesion along the vertebrae in the mediastinum.

Just to be consistent and to stick to the observation concerning the left jugular vein, I make my guess that that is where the trouble started, but admit that the whole thing may turn out to have been due to a neoplasm.

DR. JOST MICHELSEN: With brain abscess, how do you explain the cerebrospinal findings—the low pressure, the low protein and so forth?

DR. DOCK: The spinal fluid could be quite normal if the abscess were deeply placed in the brain. It seems to have been well walled off. Furthermore, a temporal-lobe abscess may have quite normal spinal fluid.

DR. MICHELSEN: In the acute stage?

DR. DOCK: Have we evidence that it was acute? The patient had fever only at the end. These varying palsies suggest an abscess, which does not actually destroy anything but from time to time causes disturbances that may be associated with edema or something of that sort. That is a long chance, but this is a puzzling case.

DR. JAMES B. AYER: I know the case, but I think you put too much stress on the left jugular compression.

DR. DOCK: So do I, after seeing the x-ray film of the chest.

DR. AYER: That may be normal. I think it was too bad it was in there.

DR. DOCK: I think it was good, because it gave me a point to build on.

DR. G. COLKET CANER: One of the striking points was the loss of 50 pounds early in the illness before any fever was reported; this seems to suggest neoplasm, much more than an infectious process, but I should not know where it started.

DR. DOCK: Weight loss may be marked with intracranial disease and with change of personality. One of the problems, if you try to explain this on the basis of neoplastic disease, is that the cerebral symptoms came and went. I should expect cerebral metastases to give progressive symptoms rather than transient ones.

DR. AYER: Not infrequently, metastases give changing symptoms.

DR. WYMAN RICHARDSON: May I ask if the shadow in the mediastinum looks like the thyroid gland?

DR. HOLMES: It could be.

DR. RICHARDSON: Might not a tumor originating in the thyroid gland metastasize to bone, explaining backache, and later metastasize to the brain?

DR. DOCK: X-ray films of the spine were negative. With thyroid metastases to the spine, I think that one would pick them up three months after the pain started.

DR. HOLMES: I agree.

#### CLINICAL DIAGNOSES

Brain abscess?

Right-upper-lobe pneumonia.

#### DR. DOCK'S DIAGNOSES

Chronic otitis media.

Jugular thrombophlebitis.

Metastatic abscesses, paravertebral and cerebral.

#### ANATOMICAL DIAGNOSES

Carcinoma of the tail of the pancreas, with metastases to regional nodes, liver, lungs and pleura.

Endocarditis, probably marantic: aortic valve.

Multiple emboli, with secondary infarction, to brain, spleen and kidneys.

Emboli in portal vein.

Infarction, partial, of liver.

Perforation of left eardrum.

#### PATHOLOGICAL DISCUSSION

DR. MALLORY: At post-mortem examination, we found an enormous liver, full of metastases. The next finding was a large mass, which completely filled the lesser peritoneal cavity and evidently arose from the tail of the pancreas and had secondarily involved the stomach and the colon. There were pulmonary metastases, and the shadow in the x-ray film arose from lymph nodes in the neighborhood of the trachea. When we opened the heart, we found an acute endocarditis of the mitral valve, apparently of the vegetative type. The brain showed embolic areas of infarction, but no tumor metastases. The endocarditis remains a problem. Grossly, it was suggestive of acute bacterial endocarditis. Blood cultures taken the day before death and at autopsy, however, were sterile. Attempts to culture the vegetations themselves provided us with a healthy growth of non-hemolytic streptococci, colon bacilli and *Bacillus subtilis*. One can take one's choice or discard them all. The sections of the heart valve showed no bacteria whatever, and practically no inflammatory reaction. It seemed to be a perfectly pure thrombotic vegetation, with no inflammatory reaction, and no fibrosis or organization at its base. A further complication in the interpretation was provided by finding one really good Aschoff nodule in the myocardium, so that what kind of endocarditis this was, I do not know. We have

no proof that it was bacterial. It does not in itself look rheumatic, but the Aschoff body suggests that etiology. Moreover, I do not like the idea of rheumatic vegetations that throw off multiple emboli. Whether there is such a thing as marantic endocarditis, I have never been certain. This case may be so classified if one believes it to exist. At all events, it is by no means rare for patients dying with metastatic neoplasm to develop a terminal endocarditis. It is comparatively uncommon for this to produce multiple infarcts of significant size. There were infarcts in both spleen and kidney, quite fresh ones. There was no evidence of old abscess or stone in the kidney.

DR. DOCK: Were the lateral sinuses and the jugular vein all right?

DR. MALLORY: Yes; there was only a perforation in the left ear drum, and no mastoiditis.

Finally, a most unusual condition, which probably played no part in the symptomatology, was found in the portal circulation. A thrombus had formed in the splenic vein, where it was involved by the tumor of the pancreas. From this, fragments had broken off and had been swept as emboli into the portal circulation, where they were found in the intrahepatic portal radicles. Partial or incomplete infarction of many focal areas in the liver had resulted, although the hepatic arteries had, of course, prevented complete infarction.

## CASE 28032

### PRESENTATION OF CASE

A sixty-three-year-old housewife was admitted complaining of shortness of breath.

For sixteen years, she had had diabetes, which was controlled by diet in addition to 10 units of insulin daily. The insulin therapy, however, was stopped, one year before entry, on the advice of her physician. Three months before admission, while the patient was pumping water, a sudden, severe, oppressive crushing pain occurred beneath the lower sternum and radiated straight through to the back and down the inner aspects of both arms as far as the elbows. She became anxious, extremely short of breath and covered with perspiration, and the heart beat rapidly. Rest gave no relief. The patient did not mention the pain to her family, but went in to supper, after which the pain became worse. Nausea and vomiting developed, and she called her physician, who put her to bed. The pain, however, remained unchanged for two days, after which it disappeared. The patient remained in bed for two weeks, but was afterward dyspneic on slight exertion. Two

weeks before admission, she became orthopneic, at first being able to sleep on two pillows, then unable to sleep except when she sat almost straight up in a chair. During the night, she had several attacks of waking with a sense of suffocation and gasping for breath for about ten minutes. Four days after the appearance of orthopnea, the ankles began to swell, the edema gradually extending to the knees.

For many years, the patient had had brief attacks of precordial pain frequently radiating down the arms; there was no history of rheumatic fever, hypertension or weight loss. For several years, she had had occasional attacks of sharp squeezing pain beneath the right costal margin lasting two to ten minutes and associated with a slight swelling in that area. The pain and swelling were relieved by the taking of food. Twenty-eight years prior to admission, she had an enucleation of the right eye for glaucoma.

Physical examination revealed a pale, poorly nourished, slightly cyanotic woman sitting up in bed, with dyspnea, and complaining of substernal distress. There was marked pitting edema of both lower legs and of the sacrum. A deep 2-cm. scar was present on the sole of the right foot. The right eye was absent. The left eye was myopic, but examination of the pupil was negative. There was vacuolar degeneration of the lens. The disk was flat and showed a myopic crescent, and scattered about it were hemorrhages and exudate. External ocular movements were normal. The patient was edentulous and had a coated tongue. The tonsils were buried. The chest was somewhat barrel shaped, expansion was limited, and the accessory respiratory muscles were used extensively. There was dullness to flatness, with decreased breath sounds and moist rales, at both bases. The diaphragm was high, with limited excursion. The heart was enlarged to the left, but could not be outlined by percussion. The point of maximum intensity was felt 1.5 cm. to the left of the mid-clavicular line. Retromammary dullness was increased. The sounds were of good quality; there were no murmurs, and the rhythm was normal. The peripheral vessels were tortuous and sclerotic. No pulsations could be made out in either dorsalis pedis or posterior tibial arteries. Reflexes could not be obtained in the lower extremities, and there was impaired vibratory sense in both legs. Examination of the abdomen was negative.

The rectal temperature was 100°F., the pulse 98, and the respirations 20. The blood pressure was 130 systolic, 80 diastolic.

Examination of the urine showed a specific gravity of 1.022, a ++ test for albumin, a + test for

sugar, and an occasional red cell, 30 white cells and an occasional hyaline cast per high power field. The blood showed a red cell count of 4,260,000 with 74 per cent hemoglobin, and a white-cell count of 9500 with 60 per cent polymorphonuclears. The serum nonprotein nitrogen was 28 mg and the protein 5.6 gm per 100 cc. The fasting blood sugar was 374 mg per 100 cc. A blood Hinton reaction was negative.

On the night of the day of admission, the patient complained of slight substernal oppression. At 5 o'clock the following morning, she seemed unusually drowsy and at 6 o'clock could not be roused. There were signs of an early left sided hemiplegia. The heart sounds were poor, and the blood pressure 70 systolic, 40 diastolic. The respirations were shallow and weak. The rectal temperature was 103°F, the pulse 80, and the respirations 35.

The patient rapidly failed and died on the third hospital day. A short while before death, an electrocardiogram showed a PR interval of 0.16 second, a ventricular rate of 100 and normal rhythm. The ST intervals in Leads 1 and 2 were depressed, and those in Lead 3 were elevated. There was moderate left axis deviation.

#### DIFFERENTIAL DIAGNOSIS

**DR PAUL D WHITE** Dyspnea was this patient's chief complaint.

We have shown in the last year or two, in association with Dr. Howard F Root,\* that coronary heart disease is much commoner in diabetic than in nondiabetic patients.

It is a little unusual for pain to radiate through to the back in acute coronary occlusion.

It is not likely that the rapid beating of the heart was responsible for such terrific pain as that described here. That is probably a secondary symptom due to the pain or whatever caused the pain, and not the primary cause of the pain itself. Persons who have coronary insufficiency may develop severe pain, but hardly of this severity, when they have paroxysmal tachycardia. It is not likely that the perspiration was due to apprehension alone. This patient was sturdy, and could stand pain and did not want to give in to it.

I should like to be sure that nausea and vomiting developed before and not after medication. Did the physician give her morphine?

**DR BENJAMIN CASTLEMAN** There is a letter from her doctor stating that digitalis was given; there is no suggestion that he administered morphine.

**DR WHITE** The pain gradually subsided. Two weeks in bed is a short time for any episode as severe as this. That may indicate an unusually rapid recovery, or may have been due to refusal on her part to stay in bed more than that length of time. Whatever happened was followed by the appearance of dyspnea on slight exertion, which suggests that the patient got up too soon.

Three months after the onset of the acute illness, she became orthopneic, which means a progression of the dyspnea.

She had right sided heart failure rapidly following extensive left-sided heart failure; that can be the only interpretation of this sequence of events. That the painful episode was what set off the congestive failure, we cannot be absolutely certain, but it looks so.

"For many years, the patient had had brief attacks of precordial pain frequently radiating down the arms." This suggests that she had been somewhat ailing for a long time but apparently not enough so to consult a physician. I should like to know more about the attacks of precordial pain. The precordium is quite extensive, and there is a good deal of difference in clinical significance between substernal pain and that at the cardiac apex or left breast part of the precordium. The story sounds like angina pectoris, probably on effort.

"For several years, she had had occasional attacks of sharp squeezing pain . . . The pain and swelling were relieved by the taking of food." That suggests hyperacidity and cardiospasm, a definite digestive disorder.

"Physical examination revealed a pale, poorly nourished, slightly cyanotic woman sitting up in bed, with dyspnea, and complaining of substernal distress." I have mentioned before that patients with dyspnea usually do not have substernal distress—in short, that they do not have myocardial and coronary insufficiency at the same time; hence the substernal distress may have been due to cardiospasm or other noncardiac causes.

"Retromammary dullness was increased." This is important if true. Of course, marked increase in retromammary dullness suggests aneurysmal dilatation of the aorta in a cardiovascular patient. "There were no murmurs, and the rhythm was normal." This statement is very important in ruling out valvular disease.

The blood pressure was normal, there is no suggestion of hypertension. Apparently there was not a drop from a high blood pressure.

"The peripheral vessels were tortuous and sclerotic. No pulsations could be made out in either dorsalis pedis or posterior tibial arteries." In dia-

\*Root H F, Bland E F, Gordon W H and White P D. Coronary atherosclerosis in diabetes mellitus: a postmortem study. *JAMA* 113: 30, 1939.



betic patients, one may find an obliterating sclerosis, which could cause these signs.

We can now begin to build up a story for a dissecting aortic aneurysm, with sudden anterior chest pain referred to the back, increase in retro-manubrial dullness, and absence of pulsations in the feet.

"The temperature was 100°F." There may be slight fever due to congestive failure alone without the need of making an additional diagnosis of infarction or infection anywhere, but there is usually some complication in febrile patients with congestive heart failure to explain the fever.

Left-axis deviation is the most significant finding in the electrocardiogram. Nevertheless, change in the ST intervals may also be of some consequence.

In summary, we know that this patient had diabetes. She had extensive and severe arteriosclerosis, including the coronary arteries and probably the aorta. She had cardiac enlargement and failure. These things are quite clear. The points in doubt are the cause of the acute attack three months before she died and the cause of the final episode. It is too easy to diagnose myocardial infarction as explaining both, but nevertheless,—because it is most probable, even though too easy,—I shall give that as my first diagnosis, realizing that I am not at all sure of being correct. Dissecting aneurysm is a possibility. A dissection of the aorta is commoner in a person who is hypertensive, but it is not limited to hypertensive patients. It is conceivable that both conditions could be present in a patient of this sort, with a high degree of coronary-artery damage and secondary myocardial effects from it. Whether that is the only condition to be found is open to some doubt. Sudden intense pain radiating to the back, with the cutting off of the circulation to the feet, is strongly suggestive of dissecting aortic aneurysm, but the faulty peripheral circulation may be secondary to diabetic sclerosis of the vessels. The patient had had some indigestion. It is quite common for gallstones to be associated with coronary-artery disease, so that I should not be surprised if gallstones were present in this patient, although they were probably not responsible for the original severe attack of pain. Nausea and vomiting are commoner with gallstone colic than with attacks of coronary thrombosis, but once in a while an attack of biliary colic precipitates heart failure in a patient who has a good deal of heart disease to start with. I do not believe, however, that a digestive upset could explain the original attack. I should vote for the probability of myocardial in-

farction in general, but admit the possibility of a dissecting aortic aneurysm.

A PHYSICIAN: How about the terminal event?

DR. WHITE: I should think that a fresh infarction could explain the terminal event, although if there had been a dissecting aortic aneurysm to explain the first episode, rupture of the aorta could account for the final illness. A cerebrovascular accident may also have occurred. It does not seem likely that the final episode was diabetic coma per se. I do not know whether it is possible to have hemiplegia due to diabetic coma complicating severe cerebral vascular disease without complete occlusion of a vessel. I cannot say whether fresh coronary thrombosis was the cause of death, but I think it was.

DR. HOWARD B. SPRAGUE: Do you think she might have had mural thrombus with embolism?

DR. WHITE: I wrote it down as a possibility, but I do not consider it an essential diagnosis in a person with so much cerebrovascular disease.

DR. CASTLEMAN: Can you explain the hemiplegia solely on the basis of arteriosclerosis without thrombosis or embolism?

DR. WHITE: Yes; I think that I have been caught several times on terminal events of such a nature. In a similar way, abnormalities of the electrocardiogram can be explained by low pressure in a coronary circulation that is already at fault, without fresh coronary occlusion. Several times, I have diagnosed cerebral embolism in the presence of weakness on one side of the body or the other without finding such a condition at autopsy.

#### CLINICAL DIAGNOSES

Coronary occlusion.  
Cardiac failure.  
Generalized arteriosclerosis.  
Diabetes mellitus.  
Cerebral accident, with left hemiplegia.

#### DR. WHITE'S DIAGNOSES

Diabetes mellitus.  
Extensive arteriosclerosis, coronary, cerebral and peripheral.  
Coronary occlusion, with myocardial infarction, old and new.  
Congestive heart failure, left ventricular, followed by right.  
Hemiplegia due to cerebral vascular insufficiency.  
Dissecting aortic aneurysm, with terminal rupture?

## ANATOMICAL DIAGNOSES

Embolism of middle cerebral and posterior cerebral arteries, right and left.  
Cerebral infarcts, bilateral, recent.  
Coronary thrombosis, old.  
Cardiac infarction, healed.  
Chronic passive congestion of liver and spleen  
Hydrothorax, ascites and peripheral edema.  
Arteriosclerosis, generalized, marked.

## PATHOLOGICAL DISCUSSION

DR CASTLEMAN: This patient was in severe failure, as shown by a liter of fluid in the abdomen and as much more in each chest cavity. The liver showed signs of chronic passive congestion. The heart weighed only 325 gm., was slightly dilated, and showed old myocardial infarction on the posterior aspect of the left ventricle and diffuse scarring throughout the myocardium. That was confirmed by microscopic sections, which revealed scarring in every microscopic field, a characteristic finding in almost every case of angina pectoris. All the coronary vessels were severely sclerotic—almost rigid tubes with extensive calcification. The left descending branch was completely obliterated by an old thrombus, and beyond it was another thrombus that was more recent, which would fit the episode of three months before entry. The orifice of the right coronary artery was almost completely covered by an atherosclerotic plaque, so that very little blood was getting to the heart muscle. No mural thrombus was noted. In the brain, there was an occlusion of the right middle cerebral artery beyond the openings of the lenticular striate branches, and

an infarct of the right parietal lobe to correspond to that distribution. The infarction was very recent, and the occluding thrombus or embolus looked older than the infarct. I believe that it was an embolus, and the fact that we also found two recent lesions in each occipital lobe is more evidence that the process was embolic. The source could not be determined, although there may have been a few tiny mural thrombi on the endocardium that were not noticed at the time of autopsy. There was severe arteriosclerosis of the aorta, but no dissection.

DR. WHITE: The slight substernal oppression that was complained of the night before the patient died may have been an attack of angina pectoris.

Did she have gallstones?

DR CASTLEMAN: The gall bladder was completely obliterated, apparently from old chronic inflammation.

Is it not true, Dr. White, that if a patient is in heart failure one would not expect a dissecting aneurysm?

DR. WHITE: Yes; but this patient was not in heart failure three months ago. The important point was the explanation of the pain at that time.

DR CASTLEMAN: Do any of the patients with healed dissecting aneurysm die in heart failure?

DR. WHITE: I believe that, in a heart so seriously involved as this, one would prefer the initial diagnosis of coronary heart disease with angina pectoris, but the severe shock of a dissecting aneurysm might precipitate heart failure.

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established in 1828

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND  
PUBLISHED UNDER THE JURISDICTION OF THE COMMITTEE  
ON PUBLICATIONS

Official Organ of  
THE MASSACHUSETTS MEDICAL SOCIETY  
and  
THE NEW HAMPSHIRE MEDICAL SOCIETY

## EDITORIAL BOARD

Joseph Garland, M.D.	Stephen Rushmore, M.D.
William B. Breed, M.D.	Henry R. Viets, M.D.
George R. Minot, M.D.	Robert M. Green, M.D.
Frank H. Lahey, M.D.	Charles C. Lund, M.D.
Shields Warren, M.D.	John F. Fulton, M.D.
George L. Tobey, Jr., M.D.	A. Warren Stearns, M.D.
C. Guy Lane, M.D.	Dwight O'Hara, M.D.
William A. Rogers, M.D.	Chester S. Keefer, M.D.

## ASSOCIATE EDITORS

Thomas H. Lanman, M.D.	Donald Munro, M.D.
Henry Jackson, Jr., M.D.	
Walter P. Bowers, M.D., EDITOR EMERITUS	
Robert N. Nye, M.D., MANAGING EDITOR	
Clara D. Davies, ASSISTANT EDITOR	

SUBSCRIPTION TERMS: \$6.00 per year in advance, postage paid, for the United States (medical students, \$3.50 per year); Canada, \$7.04 per year, Boston funds; \$8.52 per year for all foreign countries belonging to the Postal Union.

MATERIAL for early publication should be received not later than noon on Friday.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston, Massachusetts.

## WAR AND VENEREAL DISEASE

THE country is at war. For ultimate victory, among other items, the fighting services must have not only planes, guns and tanks, but proper food and good health; and of the factors causing disability among soldiers and sailors no one has been more important than venereal disease. As a complication of war, it has accompanied armies for centuries. Wherever armies have gone, the specter of venereal disease has stalked, and has immobilized manpower, often on a large scale. Today, the army camp, with its motorized equipment of modern warfare, is accompanied by the dangers of the trailer camp, as pointed out elsewhere in this issue of the *Journal*. And yet the past few years have indicated that much can be accomplished in the control of this scourge. If

one studies the curve of the venereal-disease rate of the United States Army over the last fifty years, one finds a gradual and striking reduction from a peak of approximately 160 per 1000 in 1902 to a low of about 36 per 1000 in 1939.<sup>1</sup> In England, the total venereal-disease rate in the army has steadily fallen, and for the first five months of 1941 was only 8.4 per 1000, with the ratio of gonorrhea to syphilis remaining about 8:1.<sup>2</sup> In this country, in two large maneuver areas where venereal-disease control has been studied, gonorrhea was about four and ten times as frequent as syphilis.<sup>3</sup>

The incidence of venereal disease among selectees has been surprisingly low, and of course, no person with an active case is admitted to the Army or Navy. Moreover, steps are being taken to control these diseases even more effectively than in the last war. Although the medical officers of the Army and Navy are responsible for the prevention and effective treatment of disease, they need assistance to fulfill the requirements of modern preventive medicine. Thus, in July, 1941, Congress passed the May Act, which provides for the control of prostitution in such areas around military and naval establishments as are designated by the Secretary of War and the Secretary of the Navy. The Federal Bureau of Investigation has been made responsible for the enforcement of this law.

In August, 1941, the Secretary of War, through the Chief of Staff, issued an order regarding the prohibition of prostitution within reasonable distance of military establishments. This order placed the responsibility for the health and welfare of personnel on the commanding officer of each post or camp and outlined the procedure of obtaining local co-operation for the remedying of bad conditions, as well as that to be followed if local co-operation failed. To achieve the full effect of the May Act, the commanding officer may obtain aid from both the Federal Security Agency and the Adjutant General of the Army.

In addition, on October 2, 1941, the Federal Security Agency established the Division of Social Protection, whose purpose is primarily to "promote the public health by the reduction of venereal

disease through the repression of commercialized prostitution." The United States Public Health Service and the Defense, Health and Welfare Services are likewise under the Federal Security Agency, and both have departments dealing with venereal disease, as well as other health conditions. Furthermore, the Army and Navy Committee on Welfare and Recreation, the American Social Hygiene Association and various other agencies are in a position to aid in various phases of the problem.

The machinery for the control of venereal disease and for the prevention of its resulting disability seems to exist, even with the very rapid expansion of the military and naval forces that is bound to occur in the present emergency. The full efficiency of this machinery, however, will be attained only by the proper co-ordination of the various agencies participating in this program.

#### REFERENCES

- 1 Editorial. Plain words about venereal disease. *J A M A* 117 1890 1897 1941
- 2 Incidence of venereal diseases. *Brit M J* 2 208 1941
- 3 Price A B and Weber F J. Control of the venereal diseases in civilian areas adjacent to concentrations of armed forces. *Am J Pub Health* 31 912 916 1941

### ACUTE INTESTINAL OBSTRUCTION

ACUTE intestinal obstruction is one of the major problems of any surgical service and contributes to a large number of deaths. For the last five years in Massachusetts, intestinal obstruction has annually accounted for an average of 4 deaths per 100,000 population. Of course, not all these deaths resulted from acute conditions, but many other deaths from acute obstruction were probably not included, being masked under such diagnoses as appendicitis and salpingitis. If seen in the first six to twelve hours, no patient should die from simple obstruction due to adhesive bands, from gallstone obstruction or from intussusception, and very few should fail to react favorably to treatment for most other types of obstruction if they are intelligently handled by the physicians who first see them. In the past, a difficulty has been the obscurity of the diagnosis, because of the lack of localizing or of pathognomonic symptoms in the early curable stage of the illness. The diagnosis has been based, in most cases, purely on the his-

tory and abdominal palpation, accompanied, all too frequently, by the time-consuming and exhausting therapeutic test of multiple enemas.

Aids have recently been developed that greatly simplify and standardize the early diagnosis of acute obstruction. The outstanding one is x-ray examination of the abdomen by the so-called "flat plate" or "scout plate." Such an examination does not trouble the patient and gives definite information very early in the condition. To be effective, however, hospitals must be organized so that such plates can be read promptly. A delay of several hours in making a diagnosis of acute obstruction largely negates the advantage afforded by x-ray films of this type.

In this issue of the *Journal* is a paper concerning another very much neglected aid to such a diagnosis. Abdominal auscultation has been used in a relatively desultory fashion for years, but few physicians or surgeons have paid enough attention to it to perfect their interpretation of abdominal sounds. Only recently have adequate discussions of this subject come into prominence in surgical texts. One of the best is by Wangenstein,<sup>1</sup> who states, in a section on the diagnosis of acute intestinal obstruction:

*Auscultation* — The chief value of auscultation in an acute intestinal lesion relates to the determination of whether *intestinal colic* is absent or present. The repeated audition of borborygmi with the stethoscope at the acme of the pain of which the patient complains establishes the pain as being caused by the intestinal contraction. To be certain, borborygmi or intestinal noises may be heard in other disorders, but it is the intimate time relationship between noise and pain which identifies its origin. A noisy abdomen does not therefore indicate the presence of a mechanical obstruction of the bowel, such a finding only denotes the state of activity of the intestine. A silent abdomen indicates absence of intestinal activity, a noisy abdomen without *intestinal colic* signifies that the bowel is hyperactive.

Other excellent statements concerning auscultation are found in Vaughan's<sup>2</sup> section on appendicitis and Ochsner's<sup>3</sup> section on acute intestinal obstruction in *Nelson New Loose Leaf Surgery*. However, Lewis and Fier,<sup>4</sup> writing on appendicitis in Christopher's *Text Book of Surgery*, do not mention auscultation, nor did Hertzler,<sup>5</sup> writing

on diseases of the peritoneum, and Cutler and Scott,<sup>6</sup> on postoperative complications, mention it in the somewhat older text, Graham's *Surgical Diagnosis*. In the latter book, however, Richardson,<sup>7</sup> in the section on the clinical manifestations of acute intestinal obstruction, makes the following significant statement, "On auscultation the gurgling due to hyperactive peristalsis is usually heard, a finding which is very useful in distinguishing mechanical from paralytic obstruction."

It should be noted that Wangensteen emphasizes a very important distinction in interpretation that is not made clear by Dr. Stevens, namely, that the loud and frequent sounds of hyperperistalsis mean hyperperistalsis—they do not necessarily mean obstruction. On the other hand, Dr. Stevens's courageous description of his three failures and one success should serve to teach others, who, like him, see such cases only rarely, concerning the possibilities in this field.

The interpretation of intestinal sounds, however, is not too simple and cannot be taught from a book or an article. There is a wide variation of intensity and frequency in relation to the physiologic state of digestion, with greater activity one or two hours after meals than at other times. It is imperative that each physician who is to use this diagnostic aid study normal intestinal sounds at all times of the day so that he can learn what is abnormal.

Another aid in intestinal obstruction is the Miller-Abbott or double-lumen tube. But this tube is used more to determine the location of an obstruction and to treat certain types of obstruction than to help in the original diagnosis. In particularly difficult cases in which a Miller-Abbott tube is thought to be near an obstruction, a small amount of thin barium may be introduced through it to outline the lesion. Ordinary barium examinations, however, should *never* be undertaken in the presence of acute or partial obstruction, since masses of barium are extremely difficult to handle if a resection is performed or if the intestine is opened for any purpose. If mineral oil happens to be mixed with the barium, as frequently occurs in these cases, a thick tenacious gummy mass is formed. Spilling of even a very small amount

of this mixture into the peritoneal cavity almost invariably results in a fatal peritonitis.

Acute intestinal obstruction, except in those cases in which strangulation takes place, seldom causes severe immediate pain; furthermore, the pain is not localized. Any new type of abdominal pain should be viewed with suspicion. After palpation, one should listen to the intestinal sounds, and then, if there is the least doubt about what is going on, an x-ray examination without barium should be performed. With this evidence, diagnosis is usually surprisingly easy and the results of treatment extraordinarily good, because patients with obstruction are cared for early—when they should be.

#### REFERENCES

1. Wangensteen, O. H. *The Therapeutic Problem in Bowel Obstruction: A physiological and clinical consideration*. 360 pp. Springfield, Illinois: Charles C Thomas, 1937. P. 105. Intestinal obstruction. In *Christopher's Text Book of Surgery by American Authors*. 1695 pp. Philadelphia: W. B. Saunders Co., 1939. Pp. 1127-1158.
2. Vaughan, R. T. Appendicitis. In *Nelson New Loose-Leaf Surgery*. Pp. 297-342. Vol. V. New York and London: Thomas Nelson and Sons. P. 323.
3. Ochsner, A. Surgery of the intestine. In *Nelson New Loose-Leaf Surgery*. Pp. 243-296. Vol. V. New York and London: Thomas Nelson and Sons. P. 273.
4. Lewis, D., and Firor, W. M. Appendicitis. In *Christopher's Text Book of Surgery*. 1695 pp. Philadelphia: W. B. Saunders Co., 1939. Pp. 1113-1127.
5. Hertzler, A. E. Diseases of the peritoneum. In *Graham's Surgical Diagnosis*. Vol. II. 871 pp. Philadelphia: W. B. Saunders Co., 1930. Pp. 589-626.
6. Cutler, E. C., and Scott, W. J. M. Post-operative complications. In *Graham's Surgical Diagnosis*. Vol. I. 919 pp. Philadelphia: W. B. Saunders Co., 1930. Pp. 128-208.
7. Richardson, E. P. Diseases of the appendix, small intestine and colon. In *Graham's Surgical Diagnosis*. Vol. II. 871 pp. Philadelphia: W. B. Saunders Co., 1930. Pp. 627-715.

#### MEDICAL EPONYM

##### McBURNAY'S POINT

Charles McBurney (1845-1913) reported his "Experience with Early Operative Interference in Cases of Disease of the Vermiform Appendix" in the *New York Medical Journal* (50: 676-684, 1889) and described his famous point thus:

The *exact* locality of the greatest sensitiveness to pressure has seemed to me to be usually one of importance. Whatever may be the position of the healthy appendix as found in the dead-house—and I am well aware that its position when uninfamed varies greatly—I have found in all of my operations that it lay, either thickened, shortened or adherent, very close to its point of attachment to the caecum. This, of course, must, in early stages of the disease, determine the seat of greatest pain *on pressure*. And I believe that in every case the seat of greatest pain, *determined by the pressure of one finger*, has been very exactly between an inch and a half and two inches from the anterior spinous process of the ilium on a straight line drawn from that process to the umbilicus. This may appear to be an affectation of accuracy, but, so far as my experience goes, the observation is correct.

R. W. B.

## MASSACHUSETTS MEDICAL SOCIETY

## STATED MEETING OF THE COUNCIL

A stated meeting of the Council will be held in John Ware Hall, Boston Medical Library, 8 Fenway, on Wednesday, February 4, 1942, at 10:30 a.m.

*Business*

- 1 Call to order at 10:30 a.m.
- 2 Presentation of record of meeting held October 1, 1941, as published in the *New England Journal of Medicine*, for November 6, 1941.
- 3 Report of Auditing Committee and of Treasurer
- 4 Reports of standing and special committees
- 5 Appointment of Delegates
  - (a) To the House of Delegates, American Medical Association, for two years from June 1, 1942
  - (b) To the annual meetings of the five New England state medical societies in 1942
  - (c) To the Annual Congress of the American Medical Association on Medical Education and Licensure at the Palmer House, Chicago, February 16 and 17, 1942
- 6 Such other business as may lawfully come before the meeting

MICHAEL A. TIGHE, M.D.  
Secretary

The president, Dr. Ober, requests that all councilors at attending the meeting remain until the business of the meeting is finished.

\* \* \*

IMPORTANT ADDENDA TO BE CONSIDERED  
BY THE COUNCIL

## COMMITTEE ON PUBLIC RELATIONS

*Subcommittee on Tax-Supported Medical Care*

The special committee having this matter in hand will offer the following report:

**Medical Relief** Of the total bill for medical care nearly a quarter is now paid from tax revenues.

The quality of hospital medical care is effectively supervised by the professional staff. The quality of medical care to the indigents and old age recipients outside hospitals is too often below acceptable standards.

The Massachusetts Medical Society believes that it should endeavor to improve these standards and offers its services in the interest of better distribution of medical care in this field.

If the physicians of a given locality can agree among themselves to formulate and to participate seriously in a plan adapted to the medical needs and medical and economic resources of their community, the state laws and the regulations of the State Department of Public Welfare make it possible for the indigent patient to choose his own physician and for the physician to treat his own patients, with payment for his services supplied from public funds. Although the local public welfare official is responsible for providing necessary medical care for indigent persons the determination of medical needs should now be made with the advice of the medical profession.

All physicians should be encouraged to participate in this service.

For the purpose of maintaining orderly, practical and logical thinking on the subject of medical welfare policies, the following points must be kept in mind. Under various Massachusetts laws local welfare officials are empowered to provide medical care on a salary basis or on a fee for service basis, consequently, the indigent patient may or may not have the right of free choice of physicians, according to the procedure adopted in any given locality. In addition in cases which receive reimbursement from the State their local welfare departments must be operated under the rules and regulations promulgated by the State Department of Public Welfare. It should also be noted that the local welfare official is legally responsible to his community and to the State, for the entire conduct of his department, and he can neither delegate nor share this responsibility. He can seek and accept advice or suggestions concerning medical problems and procedures, but in the final analysis responsibility for all decisions rests solely on him.

The State Department of Public Welfare now has a full time medical adviser, and he in turn has a medical advisory committee (selected from a group nominated at his request by the Massachusetts Medical Society).

**Free Choice of Physician** The State Department of Public Welfare points out that under the law it cannot guarantee free choice of physician but draws attention to the fact that whereas in some localities it has been long standing practice to employ salaried doctors, introduction of a new medical plan has had a tendency to increase consideration of the use of the fee for service basis, since provision is made for local medical controls. The department approves the principle of free choice and is endeavoring to extend its practice.

In the majority of communities of this state (about 67 per cent), a system of free choice of physician on a fee for service basis is used by the local welfare agency. However, the department has neither the power under the law, nor does its experience to date indicate the need, to mandate communities to the extent that they must use the fee for service system rather than salary or contract. It is the major responsibility of the department to see that the scope of the program provides adequate service of high quality at reasonable cost to the taxpayers. It is believed that for the department to mandate one way or the other would introduce state medicine to the fullest extent.

**Advisory Committee** The attention of the local public welfare official is called to the value of securing the full co-operation of his county (district) medical society in the development of an approved local medical program. The State Department of Public Welfare agrees that there are advantages in the establishment of a medical advisory committee in each public welfare district and agrees to use and advocate the use of these committees and to assist in a general determination of their functions. These committees can advise and suggest and can recommend policies for supervision and administration but the responsibility for all acts and decisions must remain—and we believe should remain—in the hands of the local welfare official. State reimbursement on a local fee schedule is conditioned on the department's approval of this schedule as being reasonable for the particular community, rather than on the basis of a state-wide fee schedule. Considerable study is now being given to the question of medicines and drugs—a few localities having reached a fairly satisfactory solution of this problem.

lem,—and it can be expected that with local assistance much of the difficulty and criticism will eventually be eliminated. It is agreed that no ruling on a medical question should be made by a local welfare official in the absence of a definite recommendation by the medical advisory committee.

Attention is called to the value of an active professional advisory committee in providing the local public-welfare official with professional advice in the development and revision of the policies included in the approved local medical program, in the arbitration and discipline of professional problems and in the operation of survey boards to review and plan proper medical care for persons suffering from prolonged or disabling illnesses or presenting special or unusual medical needs. The medical advisory committee may be appointed from a list nominated for the purpose by the county (district) medical society. Where deemed advisable, related or integrated committees may be created in the same way to include representatives of other professions, institutions and laymen.

*Outpatient Departments and Clinics.* The hospital outpatient department should be used as a diagnostic center and treatment auxiliary, thereby frequently substituting this adequate service for the more costly hospital admission. Many welfare patients are admitted and kept in hospitals a week who could receive adequate studies by an outpatient diagnostic group. Savings in this field could be used to compensate more adequately the physician for better medical care.

With the establishment of the local medical plan, the department has no choice but to insist that existing clinics and other medical resources be used to the fullest, *reasonable* extent. The department does not, however, insist on the use of such resources where they fail to meet the purpose for which they were established. The department believes that where local clinics infringe on or exploit the local medical group, this is a matter for arbitration between local officials and professional groups, and not subject to state interference. Exploitation of the medical profession is unsound. It is entirely possible that, wherever local medical advisory committees really work and function, salaried practice and the overuse of clinics may be found to be increasingly less desirable medically, socially and economically. This is not to say that the solution of these problems will be merely a matter of simple evolution but rather to emphasize that their solution directly depends on the amount of thought and consideration given them.

*Co-ordination of Service Plans.* There are several methods of providing physicians' services. These methods, their costs and the results obtained vary with the locality, to a considerable extent dependent on the judgment and experience of the local welfare official and on the local conditions and needs with which he is confronted. However, nowhere in this state is there a formal, functioning mechanism that integrates and correlates all the services which are provided in a community at public expense. Current systems of expenditure for and distribution of tax-supported medical care may only *seem* to be economical. For example, if total costs were to be analyzed, it would be found that many cases are unnecessarily hospitalized thereby multiplying many times the cost of case management. Only by having the complete picture, especially regarding total individual costs, can the appropriate bodies, the welfare officials and the medical-care professions co-operate to the end that the medical needs of the individual and the community are met efficiently

as well as economically. It is hoped that machinery may be evolved which will supply this need.

Practically every plan designed to assist low-income groups or the indigent to obtain good medical care involves some reduction in the customary fees paid to physicians for similar services.

Rates must bear a reasonable relation between customary local expenditures for medical service and the ability of the public to pay.

The physician's overhead averages over 40 per cent. We realize that needs, costs and available revenue are interrelated items which affect the quality, adequacy and economy of tax-supported medical care.

Available revenue should be based on economics, and the physician should not be expected to carry the whole load. He pays his share of taxes to support welfare cases and then provides medical care to this group with monetary compensation that is, in some cases, ridiculously low.

ELMER S. BAGNALL, M.D.  
*Chairman*

#### *Subcommittee on Prepaid Medical-Care Costs Insurance*

The special committee having this matter in hand will offer the following six recommendations:

1. That permission be granted the Massachusetts Medical Service Corporation to co-ordinate its activities with the Blue Cross relative to (1) the presentation of joint contracts to subscribers and (2) administrative functioning and expense. This shall be done with each group retaining (1) its distinct independent corporate identity and (2) the right to issue separate contracts, the relation of the two corporations to be determined on a contract basis.

*Reasons:* Other medical groups have found this advantageous; industry will be interested in one contract and one payroll deduction, not two; we shall benefit by the prestige, sales approach and local experience of the Blue Cross; it is sound economically (independently, our overhead would be 22 to 24 per cent; conjointly, it may be 9 to 10 per cent).

2. That a special committee be appointed by the Executive Committee to select an executive director.

*Reasons:* The special committee has no time for this, and it would compromise our future usefulness to make a selection which might not be acceptable to a portion of the Society. Much ground must be explored: Should the director be lay or medical? Is the best man to be found locally or afield? Will the best man be found in organizations like the associated hospital or medical-service corporations of other states? To work over this ground requires a separate committee.

3. That authority be granted to the special committee to hire an actuary, provided that sufficient actuarial data are not made available to the committee through the Massachusetts Division of Insurance.

*Reasons:* Further progress requires accurate actuarial studies based on the experience of the Blue Cross in Massachusetts and that of medical-service schemes in other states. Such services should now be available to the special committee.

4. That income levels for eligibility for medical-service contracts (contrasted to medical-indemnity contracts) be set up at \$2000 for an individual and \$2500 for a family. At present, only medical-indemnity, and not medical-service, contracts shall be offered above these levels.

*Reasons* This is the median level established in Michigan. New Jersey established a \$1600 level but changed to \$2000, Buffalo started with a low level, but was required to raise it to \$1900 by the insurance commissioner, California set \$3000, Utica has no level. This level, on the basis of statistical studies includes the bulk of the low income wage earners of Massachusetts. A program with lower levels would exclude so many industrial wage earners that industry might not be interested and the program might fail. This simple basis of selection must be established or industry will not co-operate, they will not enter a complex contract calling for the establishment of varying income and family subdivision groups.

5 That contracts be prepared and presented on the following basis: (1) the quick preparation of a surgical contract for hospital surgical expense, (2) the preparation, as quickly as feasible, of a total hospital medical care contract to cover all medical fields incidental to hospital expense, (3) the careful slow preparation of a comprehensive medical-care contract covering total medical-care expense in the home, office and hospital, to be presented when the Massachusetts Medical Society so determines.

*Reasons* The final contract represents the ideal. To present it would require a year or two of study. The public may not be ready to accept the premiums of such a policy, as suggested by experience of other organizations. An early inadequate enrollment in this group would create a serious financial deficit. Industry and individuals and the statements of the Blue Cross indicate that hospital coverage for surgery or total hospital medical care is desired. Authorities state that this is the reasonable, sound approach. From this base we could educate the public to comprehensive medical care contracts, create a reserve, establish the corporation and start it functioning within a few months. There is need of urgent action which can be safely taken on the basis of all but the comprehensive medical-care contract.

6 That such sums as are indicated by the Commissioner of Insurance (presumably between \$10,000 and \$25,000) be loaned to the Massachusetts Medical Service Corporation by the Massachusetts Medical Society, and that other funds be raised by an enrollment fee from the participating physicians (to be returned to physicians enrolling within a given period of time, when, as and if the corporation is financially able to do so).

JAMES C. McCANN, M.D.  
*Chairman*

#### COMMITTEE ON MEDICAL EDUCATION

The committee has approved the following list of medical schools and colleges:

##### ARKANSAS

University of Arkansas School of Medicine, Little Rock

##### CALIFORNIA

University of California Medical School, Berkeley-San Francisco

College of Medical Evangelists, Loma Linda-Los Angeles

University of Southern California School of Medicine, Los Angeles

Stanford University School of Medicine, Stanford University-San Francisco

##### COLORADO

University of Colorado School of Medicine, Denver

##### CONNECTICUT

Yale University School of Medicine, New Haven

##### DISTRICT OF COLUMBIA

Georgetown University School of Medicine, Washington

George Washington University School of Medicine, Washington

Howard University College of Medicine, Washington

##### GEORGIA

Emory University School of Medicine, Atlanta

University of Georgia School of Medicine, Augusta

##### ILLINOIS

Loyola University School of Medicine, Chicago

Northwestern University Medical School, Chicago

Rush Medical College, University of Chicago

The School of Medicine of the Division of the Biological Sciences, University of Chicago

University of Illinois College of Medicine, Chicago

##### INDIANA

Indiana University School of Medicine, Bloomington-Indianapolis

##### IOWA

State University of Iowa College of Medicine, Iowa City

##### KANSAS

University of Kansas School of Medicine, Lawrence-Kansas City

##### KENTUCKY

University of Louisville School of Medicine, Louisville

##### LOUISIANA

Louisiana State University School of Medicine, New Orleans

Tulane University of Louisiana School of Medicine, New Orleans

##### MARYLAND

Johns Hopkins University School of Medicine, Baltimore

University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore

##### MASSACHUSETTS

Boston University School of Medicine, Boston

Harvard Medical School, Boston

Tufts College Medical School, Boston

##### MICHIGAN

University of Michigan Medical School, Ann Arbor

Wayne University College of Medicine, Detroit

##### MINNESOTA

University of Minnesota Medical School, Minneapolis

##### MISSOURI

St. Louis University School of Medicine, St. Louis

Washington University School of Medicine, St. Louis

##### NEBRASKA

Creighton University School of Medicine, Omaha

University of Nebraska College of Medicine, Omaha

##### NEW YORK

Albany Medical College, Albany

Long Island College of Medicine, Brooklyn



University of Buffalo School of Medicine, Buffalo.  
 Columbia University College of Physicians and Surgeons,  
 New York.  
 Cornell University Medical College, New York.  
 New York Medical College, Flower and Fifth Avenue  
 Hospitals, New York.  
 New York University College of Medicine, New York.  
 University of Rochester School of Medicine and Dentistry,  
 Rochester.  
 Syracuse University College of Medicine, Syracuse.

## NORTH CAROLINA

Duke University School of Medicine, Durham.

## OHIO

University of Cincinnati College of Medicine, Cincinnati.  
 Western Reserve University School of Medicine, Cleveland.  
 Ohio State University College of Medicine, Columbus.

## OKLAHOMA

University of Oklahoma School of Medicine, Oklahoma  
 City.

## OREGON

University of Oregon Medical School, Portland.

## PENNSYLVANIA

Hahnemann Medical College and Hospital of Philadel-  
 phia.  
 Jefferson Medical College of Philadelphia.  
 Temple University School of Medicine, Philadelphia.  
 University of Pennsylvania School of Medicine, Phila-  
 delphia.  
 Woman's Medical College of Pennsylvania, Philadelphia.  
 University of Pittsburgh School of Medicine, Pittsburgh.

## SOUTH CAROLINA

Medical College of the State of South Carolina, Charleston.

## TENNESSEE

University of Tennessee College of Medicine, Memphis.  
 Meharry Medical College, Nashville.  
 Vanderbilt University School of Medicine, Nashville.

## TEXAS

Baylor University College of Medicine, Dallas.  
 University of Texas Faculty of Medicine, Galveston.

## VERMONT

University of Vermont College of Medicine, Burlington.

## VIRGINIA

University of Virginia Department of Medicine, Charlottes-  
 ville.  
 Medical College of Virginia, Richmond.

## WISCONSIN

University of Wisconsin Medical School, Madison.  
 Marquette University School of Medicine, Milwaukee.

## CANADA

University of Alberta Faculty of Medicine, Edmonton,  
 Alberta.  
 University of Manitoba Faculty of Medicine, Winnipeg,  
 Manitoba.  
 Dalhousie University Faculty of Medicine, Halifax, Nova  
 Scotia.  
 Queen's University Faculty of Medicine, Kingston, Ontario.  
 University of Western Ontario Medical School, London,  
 Ontario.

University of Toronto Faculty of Medicine, Toronto, On-  
 tario.  
 McGill University Faculty of Medicine, Montreal, Quebec.  
 University of Montreal Faculty of Medicine, Montreal,  
 Quebec.  
 Laval University Faculty of Medicine, Quebec, Quebec.

JOHN P. MONKS, M.D.  
*Chairman*

## COMMITTEE ON MATERNAL WELFARE

CAUSES OF MATERNAL DEATH IN  
MASSACHUSETTS DURING 1940 (*continued*)

## HEMORRHAGE

The number of deaths due to hemorrhage (27) compares favorably with the number so allocated (36) in 1939. Table 1 presents an analysis of the cases.

*Post-partum hemorrhage.* In this series, post-partum hemorrhage was the primary cause of death in 10 cases. One case occurred in a patient with a blood pressure of 230 systolic, 120 diastolic, when she entered the hospital; however, an estimation of the record leads one to believe that the real cause of death was post-partum hemorrhage.

TABLE 1. *Deaths due to Hemorrhage.*

CAUSE	NO. OF DEATHS
Post-partum hemorrhage .....	10
Separated placenta .....	7
Placenta previa .....	5
Abortion .....	2
Inversion of the uterus .....	2
Varicosities .....	1

Two patients died of hemorrhage from two to four hours following delivery and after the attending physician had left the patient. It is unfortunate that transfusion was not used in any of these cases. One patient, on whom a cesarean section was performed, died two and a half hours after delivery. The physician was not in attendance at the time of the catastrophe, and no transfusion was given. One patient, a very unusual case, died of a profound hemorrhage two days after delivery. This, of course, could have been caused only by some type of retained placenta. In criticism, the general use of transfusion must be stimulated. Intravenous ergotrate and repeated transfusions should almost invariably ensure recovery in all cases of hemorrhage due to an atonic uterus. In none of these cases was hysterectomy attempted. This operation should always be considered in certain cases.

*Separated placenta.* Seven cases were classified as caused by separation of the placenta. Five were typical, completely separated placentas with the

characteristic tight uterus. In no case, it is interesting to note, was the Dublin method of cervical packing and the Spanish windlass employed. One case was treated as expertly as possible by a transfusion five times after hysterectomy had been performed and yet resulted fatally, which shows the inherent seriousness of this particular complication. *Accouchement forcé* was practiced in 2 cases. That this operation must never be employed—for whatever reason—has been brought out repeatedly in this column. The procedure has absolutely no place in obstetrics; it is never to be condoned.

*Placenta previa.* There were only 5 cases of placenta previa. It is interesting to note that the number of separated placentas as a cause of death is greater than the number attributed to placenta previa. Certainly, some type of separated placenta is a much commoner cause of bleeding than placenta previa. One case occurred in a patient who had had two previous cesarean sections, and in this pregnancy, a complete placenta previa and very free bleeding were present. At cesarean section, the placenta was found not only to be complete but to be a placenta accreta as well, and in spite of hysterectomy this patient succumbed. One patient with a complete placenta previa died undelivered; since she had been under observation in a hospital, there is little excuse for this fatality. It is evident from a review of these cases that transfusion does not play so important a part in the treatment of placenta previa as it should, and this must mean that some hospitals are not so adequately prepared for this procedure as they should be.

*Abortion.* There is little to be said of the abortions. Both these cases were probably criminally induced, and both patients died of massive hemorrhage. Had these patients been under good hospital care, death from this cause certainly would have been avoided.

*Inversion of the uterus.* It is very interesting that 2 cases of acute inversion of the uterus should occur in one year accompanied by massive uncontrollable bleeding that resulted in death. In neither case was the inversion suspected until after death. There is no excuse for the lack of diagnosis. Had the diagnosis been made, these patients probably would not have succumbed. Most acute inversions can readily be replaced under anesthesia, and those that cannot are readily replaced by laparotomy. It is difficult in any way to condone these deaths.

*Varicosities.* The case of the patient who died from bleeding from varicosities and vaginal tissue is most unusual. This patient was not transfused,

and so far as one can make out, oozing from the lacerated surfaces was uncontrollable.

\* \* \*

The decreased number of fatal hemorrhages is commendable. The lack of transfusion in many cases is hard to understand. If there are hospitals in Massachusetts today that are not equipped to deal with acute hemorrhage by transfusion, these hospitals are blameworthy. It is shocking to realize that 2 patients died of post-partum hemorrhage a few hours after delivery and after the medical attendants had left. Education should teach that *accouchement forcé* should never be employed in obstetrics, and emphasis on greater conservatism in the handling of separated placenta is necessary to reduce the mortality from this condition.

## POSTGRADUATE EXTENSION COURSES

The postgraduate extension courses are sponsored by the Massachusetts Medical Society in co operation with the Massachusetts Department of Public Health and the United States Public Health Service. The registration fee for the general course is \$5 00, with no fee for the course in venereal disease. All legally registered physicians of the Commonwealth are eligible to enroll. For further information, the chairman of the district committee on postgraduate instruction should be consulted.

The programs for the winter sessions are as follows:

BERKSHIRE DISTRICT PITTSFIELD	
Combined General and Venereal Disease Course*	
SUBJECT	DATE
Acute Abdominal Disease Among Infants and Children (Medical and Surgical Aspects)	
Syphilis of the Newborn. Early lesions of acquired syphilis and importance of intensive treatment, the rapid use of massive doses of arsenicals by continuous intravenous treatment; review of this modern therapy and its evaluation	March 12
Pediatrics Case Discussions and Clinics	
Cardiovascular Syphilis	March 19
Recent Advances in the Preoperative and Postoperative Care of Patients Requiring Major Surgery	
Differential Diagnosis and Treatment of Gonorrhea. Prevention and complications	March 26
Indications and Technic of Induction of Labor, with Case Histories	
Neurosyphilis as a Possible Factor in Diseases of the Nervous System	April 2
Fractures in General with Treatment	
Bone Lesions of Syphilis. Syphilitic skin lesions—differential diagnosis and treatment	April 9
Kidney Disease and Hypertension	
Lymphogranuloma Inguinale and Ducey's Bacillus Infection	April 16

\*One half of a session will be devoted to each subject

Subject to be announced

Pelvic Inflammatory Disease in the Female  
Due to Gonorrhea and Other Infections

April 23

Diagnosis and Treatment of Hemorrhage in  
Pregnancy, with Case Histories

Interpretation of Laboratory Data in the  
Diagnosis of Syphilis, Gonorrhea and  
Other Infectious Diseases

April 30

Meetings to be held at the Bishop Memorial Building,  
Thursdays, at 4:30 p.m.

Harry G. Mellen, M.D., *Chairman*  
150 North Street, Pittsfield

#### BRISTOL SOUTH DISTRICT: FALL RIVER

##### SUBJECT

##### DATE

Dermatitis and Eczema in Wartime Industry:  
Diagnosis, local treatment and preven-  
tion—cases that fall under workmen's  
compensation law and noncompensation  
cases illustrated by motion pictures and  
slides in color

January 20

Acute Abdominal Disease Among Infants  
and Children (Medical and Surgical As-  
pects)

January 27

Pediatrics: Case Discussions and Clinics

February 3

Pneumonia and Its Complications: Early  
treatment, chemotherapy

February 10

Indications and Technic of Induction of La-  
bor, with Case Histories

February 17

Diagnosis and Treatment of Surgical Diseases  
of the Stomach and Duodenum

February 24

Kidney Disease and Hypertension

March 3

Diagnosis and Treatment of Hemorrhage in  
Pregnancy, with Case Histories

March 10

Meetings to be held at the Union Hospital, Tuesdays,  
at 4:30 p.m.

Thomas L. Gettings, M.D., *Chairman*  
1042 Plymouth Avenue, Fall River

#### BRISTOL SOUTH DISTRICT: NEW BEDFORD

##### SUBJECT

##### DATE

Cardiovascular Syphilis

January 23

Differential Diagnosis and Treatment of  
Gonorrhea: Prevention of complications

January 30

Pelvic Inflammatory Disease in the Female  
Due to Gonorrhea and Other Infections

February 6

Syphilis of the Newborn: Early lesions of  
acquired syphilis and importance of in-  
tensive treatment; the rapid use of mas-  
sive doses of arsenicals by continuous  
intravenous treatment; review of this  
modern therapy and its evaluation

February 13

Interpretation of Laboratory Data in the  
Diagnosis of Syphilis, Gonorrhea and  
Other Infectious Diseases

February 20

Neurosyphilis as a Possible Factor in Diseases  
of the Nervous System

February 27

Bone Lesions of Syphilis: Syphilitic skin le-  
sions—differential diagnosis and treat-  
ment

March 6

Lymphogranuloma Inguinale and Ducrey's  
Bacillus Infection

March 13

Meetings to be held at St. Luke's Hospital, Fridays, at  
4:15 p.m.

Robert H. Goodwin, M.D., *Chairman*  
84 Spring Street, New Bedford

#### HAMPDEN DISTRICT: SPRINGFIELD

##### SUBJECT

##### DATE

Acute Abdominal Disease Among Infants  
and Children (Medical and Surgical  
Aspects)

March 4

Kidney Disease and Hypertension

March 11

Dermatitis and Eczema in Wartime Industry:  
Diagnosis, local treatment and preven-  
tion—cases that fall under workmen's  
compensation law and noncompensation  
cases illustrated by motion pictures and  
slides in color

March 18

Earache

March 25

Recent Advances in the Preoperative and  
Postoperative Care of Patients Requiring  
Major Surgery

April 1

Indications and Technic of Induction of La-  
bor, with Case Histories

April 8

Pneumonia and Its Complications: Early  
treatment, chemotherapy

April 15

Pediatrics: Case Discussions and Clinics

April 22

Meetings to be held Wednesdays at the Academy of  
Medicine, Professional Building, 20 Maple Street, Spring-  
field, at 4:00 p.m.

Alfonso A. Palermo, M.D., *Chairman*  
121 Chestnut Street, Springfield

#### MIDDLESEX EAST DISTRICT: WINCHESTER

##### SUBJECT

##### DATE

The Use of Chemotherapy in Surgical Prac-  
tice

March 10

Kidney Disease and Hypertension

March 17

Cesarean Section: Indications for use of vari-  
ous types, with case histories

March 24

Pediatrics: Case Discussions and Clinics

March 31

Pneumonia and Its Complications: Early  
treatment, chemotherapy

April 7

Head Colds and Complications

April 14

Diagnosis and Treatment of Hemorrhage in  
Pregnancy, with case histories

April 21

Acute Abdominal Disease Among Infants  
and Children (Medical and Surgical  
Aspects)

April 28

Meetings to be held in the Nurses' Home, Winchester  
Hospital, Tuesdays, at 4:15 p.m.

T. E. Caulfield, Jr., M.D., *Chairman*  
14 Church Avenue, Woburn

#### NORFOLK DISTRICT: NORWOOD

##### SUBJECT

##### DATE

Head Colds and Complications

January 15

Indications and Technic of Induction of La-  
bor, with Case Histories

January 29

Recent Advances in the Preoperative and Post-  
operative Care of Patients Requiring  
Major Surgery

February 12

Pneumonia and Its Complications: Early  
treatment, chemotherapy

February 26

Dermatitis and Eczema in Wartime Industry:  
Diagnosis, local treatment and preven-  
tion—cases that fall under workmen's  
compensation law and noncompensation  
cases illustrated by motion pictures and  
slides in color

March 12

Kidney Disease and Hypertension

March 26

Diagnosis and Treatment of Hemorrhage in Pregnancy, with Case Histories April 9  
 Acute Abdominal Disease Among Infants and Children (Medical and Surgical Aspects) April 23  
 Meetings to be held every other Thursday, at the Norwood Hospital, at 8 45 p m

Hugo B C Riemer, M D, Norwood, *Chairman*  
 Office, 128 Newbury Street, Boston

#### NORFOLK SOUTH DISTRICT QUINCY

Combined General and Venereal Disease Course

SUBJECT	DATE
Head Colds and Complications	March 2
Indications and Technic of Induction of Labor, with Case Histories	March 9
Syphilis of the Newborn Early lesions of acquired syphilis and importance of intensive treatment, the rapid use of massive doses of arsenicals by continuous intravenous treatment, review of this modern therapy and its evaluation	March 16
Diagnosis and Treatment of Hemorrhage in Pregnancy, with Case Histories	March 23
Acute Abdominal Disease Among Infants and Children (Medical and Surgical Aspects)	March 30
Interpretation of Laboratory Data in the Diagnosis of Syphilis, Gonorrhea and Other Infectious Diseases	April 6
Recent Advances in the Preoperative and Post-operative Care of Patients Requiring Major Surgery	April 13
Dermatitis and Eczema in Wartime Industry Diagnosis, local treatment and prevention—cases that fall under workmen's compensation law and noncompensation cases illustrated by motion pictures and slides in color	April 20
Pneumonia and Its Complications Early treatment, chemotherapy	April 27
Kidney Disease and Hypertension	May 4

Meetings to be held at the Quincy City Hospital, Monday at 8 30 p m

David L Belding, M D, Hingham, *Chairman*  
 Office, 80 East Concord Street, Boston

#### WORCESTER DISTRICT MILFORD

SUBJECT	DATE
Kidney Disease and Hypertension	February 24
Recent Advances in the Preoperative and Post-operative Care of Patients Requiring Major Surgery	March 3
Head Colds and Complications	March 10
Indications and Technic of Induction of Labor, with Case Histories	March 17
Acute Abdominal Disease Among Infants and Children (Medical and Surgical Aspects)	March 24
Pneumonia and Its Complications Early treatment, chemotherapy	March 31
Dermatitis and Eczema in Wartime Industry Diagnosis, local treatment and prevention—cases that fall under workmen's compensation law and noncompensation cases illustrated by motion pictures and slides in color	April 7

Diagnosis and Treatment of Hemorrhage in Pregnancy, with Case Histories April 14  
 Meetings to be held in the Nurses' Home of the Milford Hospital, Tuesdays, at 8 30 p m

Joseph Ashkins, M D, *Chairman*  
 36 Pine Street, Milford

#### WORCESTER NORTH DISTRICT FITCHBURG

SUBJECT	DATE
Pneumonia and Its Complications Early treatment, chemotherapy	March 6
Recent Advances in the Preoperative and Post-operative Care of Patients Requiring Major Surgery	March 13
The Diagnosis and Treatment of Surgical Diseases of the Stomach and Duodenum	March 20
Subject to be announced	March 27
Diagnosis and Treatment of Acute Intestinal Obstruction	April 3
Acute Abdominal Disease Among Infants and Children (Medical and Surgical Aspects)	April 10
Indications and Technic of Induction of Labor, with Case Histories	April 17
Kidney Disease and Hypertension	April 24
Meetings to be held in the Nurses' Home of the Burbank Hospital, Fridays at 4 30 p m	

George P Keaveny, M D, *Chairman*  
 62 Fox Street, Fitchburg

#### FACULTY FOR THE EXTENSION COURSES

*Dermatology* Chairman Dr John G Downing, instructors Drs John Adams, Jr, Leonard E Anderson, Bernard Appel, J Harper Blaisdell, G Marshall Crawford, Francis P McCarthy, Mildred H Ryan, Jacob H Swartz and Maurice M Tolman

*Ear Nose and Throat* Chairman Dr LeRoy A Schall, instructors Drs Charles T Porter, Lyman G Richards and John R Richardson

*Medicine* Chairmen Drs Chester S Keefer and Robert T Monroe, instructors Drs Harry A Derow, Lewis Dexter, Laurence B Ellis Maxwell Finland, Francis C Lowell and Robert W Wilkins

*Obstetrics* Chairmen Drs Meinolph V Kappius and Roy J Heffernan, instructors Drs Christopher J Duncan, M Fletcher Eades, James C Janney, Foster S Kellogg, Joseph W O Connor, Louis E Phaneuf, John Rock, Judson A Smith and Raymond S Titus

*Pediatrics* Chairmen Drs Warren R Sisson and James M Baty, instructors Drs Elmer W Barron, John A V Davies, Louis K Diamond, R Cannon Eley, Joseph Garland, Harold L Higgins, Edwin H Place and Clement A Smith

*Surgery* Chairmen Drs Richard H Sweet and Thomas J Anglem, instructors Drs Robert R Lanton, Henry C Marble and Richard H Wallace.

*Venereal Disease* Chairmen Drs Chester S Keefer and Robert T Monroe, instructors Drs David L Belding, Norman H Boyer, Earle M Chapman, Oscar F Cox, Francis R Dreuade, John H Dingle, Francis M Forster, E Parker Hayden, Rudolph Jacoby, William E Long, H Houston Merritt, Harry C Solomon, Francis M Thurmon and Paul A Young.

#### DEATHS

BRIGGS—J LYMONS BRIGGS, M D, of North Dighton, died January 3 He was in his seventy second year

Dr Briggs received his degree from Boston University School of Medicine in 1890 He was surgeon in chief at

the Massachusetts Memorial Hospitals from 1916 to 1932, and professor of surgery at Boston University School of Medicine from 1918 to 1932. He was a fellow of the American College of Surgeons and a member of the Massachusetts Medical Society, the Boston Surgical Society and the American Medical Association.

His widow survives him.

**PAINE**—MORTIMER H. PAINE, M.D., of South Hanson, died October 1. He was in his sixty-sixth year.

Dr. Paine received his degree from Tufts College Medical School in 1909. He was a former member of the Massachusetts Medical Society.

**SEARS**—HENRY F. SEARS, M.D., of Boston, died January 1. He was in his eighty-first year.

Dr. Sears received his degree from Harvard Medical School in 1887. He was assistant pathologist at the Boston City Hospital from 1888 to 1894, when he retired from active practice. He was a member of the Massachusetts Medical Society and the American Medical Association.

He is survived by two daughters and a son.

**STOWELL**—EDMUND C. STOWELL, M.D., of Marlboro, New Hampshire, died December 20. He was in his seventy-sixth year.

A native of New York, Dr. Stowell received his degree from Harvard Medical School in 1892. He was a member of the Massachusetts Medical Society and the New Hampshire Medical Society, and a fellow of the American Medical Association.

He is survived by his widow, three sons and a sister.

## WAR ACTIVITIES

### UNITED STATES ARMY

The following medical officers entered on active duty between December 28, 1941, and January 3, 1942:

Collins, Roy W., Lieut., of Colchester, Vermont: Fort Adams, Rhode Island.

Neff, Richard S., Lieut., of Boston, Massachusetts: Fort Devens, Massachusetts.

Borenstine, Joseph, Lieut., of Boston, Massachusetts: Fort Devens, Massachusetts.

Sutch, Gabriel, Lieut., of Howard, Rhode Island: Fort Devens, Massachusetts.

Scribner, Robert S., Lieut., of Haverhill, Massachusetts: Camp Edwards, Massachusetts.

Harris, Oliver J., Lieut., of Boston, Massachusetts: Westover Field, Massachusetts.

Criscuolo, Joseph A., Lieut., of New Haven, Connecticut: Fort H. G. Wright, Connecticut.

Windus, Charles E., Lieut., of New Haven, Connecticut: Army Air Base, Bangor, Maine.

Kriedberg, Marshall, Lieut., of Dorchester, Massachusetts: Army Air Base, Bangor, Maine.

Yavarow, Millin M., Lieut., of Everett, Massachusetts: Manchester Air Base, Manchester, New Hampshire.

Haselhuhn, Donald H., Lieut., of Springfield, Massachusetts: Army Air Base, Manchester, New Hampshire.

Lamb, Francis D., Lieut., of Warwick, Rhode Island: Windsor Locks, Connecticut.

Duennevier, Harold W., Lieut., of Hartford, Connecticut: Windsor Locks, Connecticut.

## CORRESPONDENCE

### PREMARITAL MEDICAL EXAMINATION

*To the Editor:* Since the passage of the Massachusetts premarital health examination law, certain problems have confronted both physicians and official agencies who have needed clarification. Among these problems is the nature of the examination required by the law. Because of the increasingly confused situation, the Department of Public Health decided to submit this question to the Attorney General's Office for legal interpretation.

We enclose a copy of the Department's letter to the Attorney General requesting interpretation of certain provisions of the premarital health examination law and copy of the Attorney General's reply. We believe the publication of this correspondence in the *Journal* will help physicians to understand more adequately the requirements of the law.

We also enclose a copy of the law which you may wish to reprint in the *Journal*.

PAUL J. JAKMAUH, M.D.  
*Commissioner of Public Health*

State House  
Boston

\* \* \*

November 21, 1941

The Honorable Robert T. Bushnell  
Attorney General  
State House  
Boston

*Dear Sir:*

There seems to be considerable confusion among many physicians concerning the nature of the examination required by Chapter 601, as amended by Chapter 697, of Acts of 1941, "An Act Relative to the Filing of Notice of Intention of Marriage."

The act requires a health examination before city and town clerks and registrars may accept filing of notices of intention of marriage. That part of the law which describes the examination required reads as follows: "Such physician, in making such examination, discover evidence of any infectious disease declared by the state department of public health to be dangerous to the public health. . . ." The examination is further defined in the next sentence, which reads, "Such examination shall include a standard serological test for syphilis. . . ."

Since the list of infectious diseases declared by the Department of Public Health to be dangerous to the public health includes some forty diseases, many of which require elaborate laboratory examinations for their detection, complete examination for each of these diseases would be impractical except in those cases in which symptoms or signs definitely indicate its presence.

Our own impression is that the law specifically requires only a laboratory test for syphilis and that any other laboratory or diagnostic test should be made only where the examination suggests an infectious disease for the detection of which an additional diagnostic test is necessary.

We wonder if you would be willing to interpret those sections of the act which bear upon the examination required, for possible release to the *New England Journal of Medicine*.

Very truly yours,

PAUL J. JAKMAUH, M.D.  
*Commissioner of Public Health*

December 1, 1941

Paul J Jakmaul, MD  
Commissioner of Public Health  
State House  
Boston

Dear Sir

You have written to ask my opinion as to the interpretation of those provisions of G L., c 207, s 20B—enacted as St 1941, c 601, s 1, and amended by St 1941, c 697—which deal with an examination to be made by a physician of the parties to an intended marriage. The pertinent provisions of the statute are as follows:

Except as hereinafter provided, such notice of intention of marriage shall not be accepted by the clerk or registrar until he has received from each party to the intended marriage a certificate signed by a qualified physician registered and practicing in the commonwealth or a commissioned medical officer on active service in the armed forces of the United States who has examined such party as hereinafter provided. If such physician, in making such examination, discovers evidence of any infectious disease declared by the state department of public health to be dangerous to the public health, he shall inform both parties of the nature of such infectious disease and of the possibilities of transmitting the same to his or her marital partner or to their children. Such examination shall include a standard serological test for syphilis and said test shall be made by a laboratory of said department or by a laboratory approved by it for such test.

The examination of such physician and the laboratory test shall be made not more than thirty days before the filing of the notice of intention of marriage.

You state that there is considerable confusion among physicians concerning the nature of the examination required by this statute, and that this arises from their uncertainty as to whether or not the parties must be examined for all infectious diseases declared by the Department of Public Health to be dangerous to the public health.

At the time St 1941, c 601, was enacted some forty infectious diseases, including syphilis, had been declared by your department, pursuant to G L., c 111, s 6, to be dangerous to the public health. You have furnished me with a list of these, which is still in force, and you inform me that for the detection of many of them an elaborate laboratory examination is necessary.

In my opinion syphilis is the only one of these infectious diseases the presence or absence of which must be determined in the manner prescribed, as a part of the examination required by G L., c 207, s 20B, as amended. I am led to this conclusion primarily by the terms of the statute, which provide that the physician shall inform the parties regarding any of these diseases of which he discovers evidence in making his examination, but which require, in the case of syphilis, that the examination shall include a specific test to be made in a specified laboratory.

Moreover, since only one laboratory test must be made seems manifest from the provision that the examination by such physician and the laboratory test should be made not more than thirty days before the filing of the notice of intention. Yet, as you inform me, many of the diseases referred to cannot be detected without various laboratory tests. This fact furnishes added support to the

conclusion that the physician is not required to determine the presence of any of the infectious diseases other than syphilis, as distinguished from merely discovering evidence of such diseases.

If the Legislature had intended the examination to determine the presence or absence of every disease in the category named, it undoubtedly would have so provided, and the expression of the requirement of a laboratory test as to one disease indicates that its omission as to the other diseases was intentional. (Cf *Boston & Albany R R Co v Commonwealth*, 296 Mass 426, 434.)

On the other hand, I believe that the physician's examination should be of such nature as to disclose any evidence of the infectious diseases referred to, which a physician could reasonably be expected to discover without a laboratory test. My opinion in this regard is based upon the manifest purpose of the statute, which is to protect the public health by measures which are reasonably calculated to deter the transmission, incident upon marriage, of the designated infectious diseases. The method adopted is a compulsory examination by a physician, including one laboratory test. The only object of the examination is to enable the physician to enlighten the parties to the intended marriage regarding the nature and transmissibility of any infectious disease, in the specified group, of which he discovers evidence. Plainly, in order to carry out the purpose of the statute, the physician's examination should be directed toward the discovery of such evidence.

Very truly yours,

ROBERT T BUSHNELL  
Attorney General

State House  
Boston

\* \* \*

#### CHAPTER 601 AS AMENDED BY CHAPTER 697, OF THE ACTS OF 1941

An Act further regulating the filing of notices of intention of marriage, and the delivery of certificates of such intention and the return of unused certificates.

**Section 1** Chapter two hundred and seven of the General Laws is hereby amended by inserting after section twenty A, inserted by section three of chapter two hundred and sixty-nine of the acts of nineteen hundred and thirty-nine, the following new section—  
Section 20B Except as hereinafter provided, such notice of intention of marriage shall not be accepted by the clerk or registrar until he has received from each party to the intended marriage a certificate signed by a qualified physician registered and practicing in the commonwealth or a commissioned medical officer on active service in the armed forces of the United States who has examined such party as hereinafter provided. If such physician, in making such examination, discovers evidence of any infectious disease declared by the state department of public health to be dangerous to the public health, he shall inform both parties of the nature of such infectious disease and of the possibilities of transmitting the same to his or her marital partner or to their children. Such examination shall include a standard serological test for syphilis and said test shall be made by a laboratory of said department or by a laboratory approved by it for such test.

Such certificate by a physician registered and practicing in the commonwealth shall read as follows—

I (name and address of physician), a registered physician of (city or town) in the commonwealth of Massachusetts declare that on (month, day, year) I examined (name and address of party) in accordance with section twenty B of chapter two hundred and seven of the General Laws. This certificate is made under the penalties of perjury.

Such certificate by a commissioned medical officer on active service in the armed forces of the United States shall read as follows:—I (name and address of physician) a (rank or title) serving in the (name of unit) of the United States on oath declare that on (month, day, year) I examined (name and home address of party) in accordance with section twenty B of chapter two hundred and seven of the General Laws of the commonwealth of Massachusetts.

Blank forms of certificates required under this section shall be furnished to city and town clerks by the department of public health.

The examination by such physician and the laboratory test shall be made not more than thirty days before the filing of the notice of intention of marriage. Whoever fails to comply with this section shall be punished by a fine of not less than ten nor more than one hundred dollars. In extraordinary or emergency cases where the death of either party is imminent or where the female is near the termination of her pregnancy, upon the authoritative request of a minister, clergyman, priest, rabbi or attending physician, the clerk or registrar may accept such notice of intention without having received the physician's certificate hereinbefore referred to.

**Section 2.** Section twenty-eight of said chapter two hundred and seven, as appearing in the Tercentenary Edition, is hereby amended by striking out, in the third and in the eleventh lines, the words "six months" and inserting in place thereof, in each instance, the words:—sixty days,—so as to read as follows:—**Section 28.** On or after the fifth day from the filing of notice of intention of marriage, except as otherwise provided but not in any event later than sixty days after such filing, the clerk or registrar shall deliver to the parties a certificate signed by him, specifying the date when notice was filed with him and all facts relative to the marriage which are required by law to be ascertained and recorded, except those relative to the person by whom the marriage is to be solemnized. Such certificate shall be delivered to the minister or magistrate before whom the marriage is to be contracted, before he proceeds to solemnize the same. If such certificate is not sooner used, it shall be returned to the office issuing it within sixty days after the date when notice of intention of marriage was filed.

**Section 3.** Section fifty-seven of said chapter two hundred and seven, as so appearing, is hereby amended by striking out, in the second and in the fourth and fifth lines, the words "six months" and inserting in place thereof, in each instance, the words:— sixty days,— so as to read as follows:—**Section 57.** Whoever performs a ceremony of marriage upon a certificate more than sixty days after the filing of the notice of intention of marriage as set forth in such certificate, and whoever having taken out such certificate and not having used it fails to return it, within sixty days after such filing, to the office issuing the same, shall be punished by a fine of not more than ten dollars.

## DISTORTED PUBLICITY

*To the Editor:* A great deal of publicity has been given to my paper in *Science* (94:2437, 1941), entitled "Clinical Achromotrichia," a preliminary report. Again, newspaper and magazine publicity is given on the paper given by me, in collaboration with Dr. Stefan Ansbacher, at a meeting of the Society of Experimental Biology and Medicine on November 12, 1941, at the New York Hospital, New York City. Photographs were shown of Dr. Ansbacher and myself in a review of medical progress by Waldemar B. Kaempffert in *Look* magazine (December 31, 1941). Many facts have been distorted and many preliminary findings that were mentioned were amplified, resulting in misrepresentation and unfair comment.

It is my purpose in this letter to ask the medical profession to realize that newspaper and magazine reports are written for the public, many times resulting in distortion and misquotes as to the facts. Further investigation is being carried on and will be published in a recognized medical journal as soon as enough laboratory and clinical results are compiled. The work that has been done and is being done is sincere, scientific and ethical. I am attempting in every way possible to take care of all requests by the medical profession for material and information concerning treatment.

It is best to state that para-aminobenzoic acid is becoming more and more difficult to obtain because of priority legislation, its mother substance being toluene, which is also necessary in the production of trinitrotoluene.

BENJAMIN F. SIEVE, M.D.

371 Commonwealth Avenue  
Boston

## BOOK REVIEWS

*Field Service Notes for Regimental Officers.* By E. M. Colwell, C.B.E., D.S.O., T.D., F.R.C.S., A.D.M.S. 16<sup>1</sup>/<sub>2</sub> cloth, 148 pp., with 29 illustrations. London: J. and A. Churchill, Limited, 1940.

This is a practical, pocket-size book with helpful directions to junior line officers of the new British Army. Officers of the Medical Corps also will find much that is worth while. Covering the duties of officers in field service and in charge of troops in billets and camps, it fills a valuable place, and should greatly aid the younger line officers in caring for the welfare, health and comfort of British soldiers under their charge.

*Dietetics for the Clinician.* By the late Milton A. Bridges, M.D. Fourth edition, thoroughly revised. 8°, cloth, 960 pp., with 83 tables. Philadelphia, Lea and Febiger, 1941. \$10.00.

This is a particularly useful book for the physician of today, for he, much more than the practitioner of the past, is expected to understand dietetics as applied to the care of the sick as well as he does pharmacology and materia medica. He must be prepared to discuss diet with his patients as he does drugs, and he must be able to write his order for a diet to the dietitian as intelligently as he writes his prescription to the pharmacist.

This volume, the fourth edition of a work previously developed and edited by the late Dr. Bridges, had been planned by him but had to be completed by his devoted collaborators, all clinicians and teachers in medicine. The result is a book fully informative and readily applicable to all dietary problems in daily practice.

# The New England Journal of Medicine

Copyright, 1942, by the Massachusetts Medical Society

VOLUME 226

JANUARY 22, 1942

NUMBER 4

## *SALMONELLA SUIPESTIFER* INFECTION IN BOSTON\*

### A Report of Eleven Cases, with Autopsy Findings in a Case of Bacterial Endocarditis Due to this Organism, and a Study of the Agglutination Reactions in this Infection

N. ERNEST GOULDER, M.D.,† MARGARET F. KINGSLAND, A.B.,‡ AND CHARLES A. JANEWAY, M.D.§

BOSTON

ALTHOUGH *Salmonella suispestifer*¶ infection has been infrequently reported in New England, it has occurred often enough in our experience to warrant emphasis on some of its peculiarities. The organism now known as *S. suispestifer* was isolated in 1885 by Salmon and Smith from swine with hog cholera. This disease of swine is now known to be caused by a filterable virus, but it is frequently complicated by an acute intestinal inflammation due to *S. suispestifer*. In 1902, Longcope<sup>1</sup> reported 2 cases of infection in man caused by an organism that was later identified by TenBroeck as belonging to the *suispestifer* group.

During World War I, *suispestifer* organisms were identified as the causative agents of a number of mild epidemics of acute gastroenteritis. In 1919, MacAdam<sup>2</sup> reported an epidemic in Mesopotamia, and Hirschfeld reported one in Serbia. Since then, many reports of similar epidemics have been published, and by 1937 Harvey<sup>3</sup> had compiled a total of 1425 cases occurring in epidemics. From these studies, it became evident that the epidemic form of infection was characterized by a brief incubation period, followed by the abrupt onset of fever, headache, abdominal pain, vomiting and diarrhea, fairly rapid recovery and a very low mortality. This organism must therefore be considered a possible etiologic agent in an epidemic of so-called "food poisonings."

Once the epidemic form of the infection became known, sporadic cases began to be reported, characterized by diverse clinical findings and by a very high mortality rate in adults. In his 1937 review, Harvey<sup>3</sup> listed approximately 70 cases of this type. Bacteremia has been noted in about 60 per cent of these sporadic cases. Clinically, the patients are often without localizing signs of infection and present a typhoidal picture characterized by an acute onset, marked fever lasting from two to ten days, headache, anorexia, vomiting, coryza, dry cough and abdominal pain. In a few cases, shaking chills, joint pains or diarrhea may occur, and children may show drowsiness, meningismus and even convulsions. As in typhoid fever, the white-cell count tends to be depressed unless the infection localizes. Although the organism is readily cultured from the blood, it is rarely observed in the stools.

When localization of the infection occurs, the lungs appear to be a site of predilection, for bronchopneumonia develops in about 30 per cent of the patients. The clinical course is characterized by high fever, daily variations in temperature as great as 2°F, and a gradual subsidence. Rarely is the organism found in the sputum; Bullowa,<sup>4</sup> in 1928, reported one such case, which was associated with lobar pneumonia. Pleural effusion, a rare finding, was reported by Boller<sup>5</sup> in 1930, by Cohen, Fink and Gray<sup>6</sup> in 1936, and by Harvey<sup>3</sup> in 1937.

Other frequent sites of localization are the bones and joints. Pyarthrosis and osteomyelitis appear in 20 per cent of the cases several days to a few weeks after the onset of the infection. The involved joint is warm, swollen and tender and, on aspiration, yields greenish fluid from which the organism may be cultured. Osteomyelitis of ad

\*From the Pathology Laboratory and the Medical Clinic, Peter Bent Brigham Hospital, the Boston Lying in Hospital, and the Department of Pathology, Department of Medicine and Department of Bacteriology and Immunology, Harvard Medical School.

†Graduate assistant in pathology, Peter Bent Brigham Hospital.

‡Bacteriologist, Peter Bent Brigham Hospital.

§Associate in medicine, Peter Bent Brigham Hospital, instructor in medicine and in bacteriology and immunology, Harvard Medical School, consulting bacteriologist, Boston Lying in Hospital.

¶Although the official name for *Salmonella suispestifer* is *S. cholerae suis*, the former name is so much more familiar that we have continued to use it in the text. For the nomenclature and classification of the commoner members of the *Salmonella* group, see Table 3.



joining bones frequently develops, and with the progression of the disease, the usual x-ray findings appear.

Purulent meningitis characterized by coma, convulsions, cervical rigidity and a positive Kernig sign was reported by Materna and Januschke<sup>3</sup> in 1925, by Kuttner and Zepp<sup>6</sup> in 1932, by Boycott and McNee<sup>7</sup> in 1936, and by Ravitch and Washington<sup>8</sup> in 1937. A case of pericarditis was described in 1936 by Cohen, Fink and Gray.<sup>5</sup> Clifton and Werner,<sup>9</sup> in 1938, presented a patient with bilateral subdural abscesses. Although the urinary tract is usually spared in these infections, mild cystitis has occasionally occurred. Other urinary-tract complications are rare, but in 1918, Neukirch<sup>10</sup> reported a case of pyelonephritis, and in 1925, Ssokoloff<sup>3</sup> described a case of perinephric abscess.

From this survey of the clinical features of *suipestifer* infections, it is apparent that although the disease tends to follow a typhoidal course, it may localize in any one of a number of sites, of which the lungs, bones and joints are the commonest. Furthermore, the infection appears oftenest under conditions that reduce the resistance of the patient. *Suipestifer* epidemics therefore tend to develop in populations already weakened by starvation and exposure, and sporadic cases often appear in people suffering from some chronic disease, such as diabetes, malaria, tuberculosis or neoplasm.\* This fact may account for the typical high mortality rate.

#### SUIPESTIFER BACTERIAL ENDOCARDITIS

The occurrence of bacterial endocarditis in *suipestifer* infections has been mentioned only in recent years. In 1931, TenBroeck, Li and Yü<sup>12</sup> reported a case of acute vegetative mitral endocarditis in a patient with blood cultures positive for *Bacterium paratyphosum* C, which belongs to the *suipestifer* group. Gouley and Israel,<sup>13</sup> in 1934, studied a case of *suipestifer* bacteremia in a four-year-old boy who developed a rough mitral murmur and later a double aortic murmur during his illness. Inasmuch as the child recovered, the clinical diagnosis of *suipestifer* endocarditis could not be proved. In 1939, Forster<sup>14</sup> reported 2 cases of fatal bacterial endocarditis that were proved to be due to *S. suipestifer* by bacteriologic studies at necropsy. One patient was a forty-seven-year-old Negro with tertiary syphilis who developed fever, leukocytosis and an apical systolic murmur of in-

creasing intensity. Three blood cultures were positive for *S. suipestifer* (American type). At post-mortem examination, the heart showed syphilitic aortitis, with extension to the myocardium, and acute ulcerative mural endocarditis of the right atrium and left ventricle. The second was a thirty-one-year-old laborer with rheumatic heart disease, who developed a spiking temperature, chills, leukocytosis and a variable diastolic murmur; seven blood cultures were positive for *S. suipestifer* (American type). At post-mortem examination, the heart showed chronic rheumatic pancarditis, with focal epicarditis, fibrosis of the aortic, mitral and tricuspid valves, and acute ulcerative mitral endocarditis. In both cases, the bacillus was recovered from the endocardial vegetations; the hearts had already been damaged by chronic disease, and the clinical course in each was stormy, with fever, leukocytosis and rapid progression. Later in 1939, Read<sup>15</sup> reported a third case of *S. suipestifer* endocarditis proved at autopsy. This occurred in a forty-nine-year-old woman with a rapidly enlarging abdominal tumor, considered to be an ovarian cyst. On paracentesis, the fluid removed from the cyst was found to contain *S. suipestifer* (European type). Septicemia due to this organism developed after operation, and systolic and diastolic murmurs appeared at the aortic area. At post-mortem examination, the heart showed acute bacterial aortic valvulitis, but there was no evidence of antecedent injury. We report below a fourth case of *S. suipestifer* endocarditis, which was studied in 1940 on the medical wards of the Peter Bent Brigham Hospital.

#### CASE REPORT

CASE 1. S. W. (P. B. H. 57907), a 58-year-old Russian-born housewife, entered the hospital on September 6, 1940, because of chills and fever of 3 days' duration. She had had an attack of "rheumatism" at the age of 26, and a heart murmur had been noted at the age of 32. For many years, she had experienced gaseous indigestion and heartburn after eating fried foods. For 4 years, she had noticed increasing shortness of breath on exertion. Three days before entry, she had a severe chill, followed by headache and fever, and accompanied by vomiting and knifelike epigastric pain. These symptoms persisted, and hospitalization was advised. One month before this episode, she had spent 2 weeks in the country, where she drank raw milk and well water, but no one else in her party had become ill.

Physical examination revealed an elderly obese woman, drowsy, mildly confused and dehydrated, who had a temperature of 103°F., a pulse of 95, respirations of 30 and a blood pressure of 120/70. The conjunctivas were injected, the pupils and fundi were normal, and the tongue was heavily coated. The heart was moderately enlarged to the left, with a prominent systolic thrill in the aortic area, and also at the apex. A loud, rough systolic murmur

\*One of the most striking examples of the course of *suipestifer* infection in a patient with neoplasm was reported by Gray<sup>14</sup> in 1936. The patient, a 36-year-old Negro with a *suipestifer* bacteremia, ran a prolonged febrile course due to abscesses in myomas of the uterus. These presumably acted as foci for reinfection. After a supravaginal hysterectomy, the patient recovered.

was heard in both areas. The pulse at the wrist was of the plateau type. Although there was slight epigastric tenderness, neither the spleen nor the liver was palpable.

The blood Hinton and Wassermann reactions were negative. The urine showed small amounts of protein at times, an occasional red blood cell and 3 to 4 white blood cells per high power field, and occasional hyaline and granular casts in the centrifuged sediment. The red-cell count fell progressively from 4,550,000 to 2,700,000, and the hemoglobin from 93 per cent to 60 per cent (Sihli). The white-cell count decreased from 21,000 to 13,000, and 90 per cent of the white blood cells in stained blood smears were neutrophils. The sedimentation rate was

x-ray films showed marked cardiac enlargement, with diffuse clouding of the lungs, suggestive of pulmonary edema. At that time, sulfapyridine therapy was started, and a total of 20 gm was given in 3 days. Because of the development of oliguria, hematuria and slight pitting edema, the drug was discontinued on the 3rd day. The temperature rose again, the signs of consolidation at the right base progressed, and abdominal distention, dyspnea and cyanosis appeared. Sulfapyridine therapy was again started on the 19th hospital day, and a total of 20.5 gm was given in the course of 3 days. Although the temperature dropped somewhat, coarse rales appeared over both lung bases, generalized edema was noted, and the

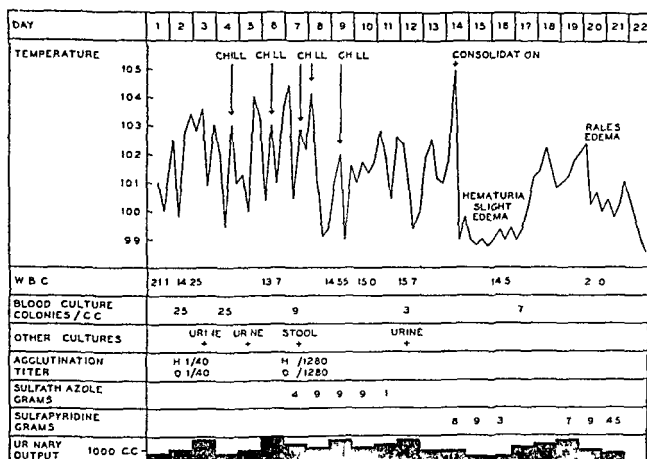


FIGURE 1 Clinical Course in Case 1

44 mm per hour (Wintrobe). Blood chemical findings included chlorides of 90 milliequivalents per liter, a distaste of 4 mg and a nonprotein nitrogen of 54 mg per 100 cc, a total protein of 5.9 gm, an albumin of 2.2 gm and a globulin of 3.7 gm per 100 cc. The icteric index was 10. The electrocardiogram showed left axis deviation and premature auricular beats. An x-ray film of the gall bladder region showed a shadow compatible with a distended gall bladder. X-ray study of the kidney and bladder regions was negative.

Five blood cultures made at various times during the hospital course were positive for *S. suis* (European type). Three urine cultures were similarly positive, and of four stool cultures, one made a week after entry yielded the same organism. On entry, the blood serum agglutinated both the H and O antigens of *S. suis* to a serum dilution of 1:40. A week later, the titer had risen to 1:1280 for both antigens.

During the first 6 days of the hospital course, the temperature fluctuated, with daily rises to a level between 102 and 104.5°F, often with chills (Fig 1). On the 7th day, the administration of sulfathiazole was started, and although 32 gm was given for 5 days, the temperature still remained high, with daily variations. On the 14th day, the temperature reached a peak of 105°F. Signs of consolidation appeared over the right lower lobe, and

venous pressure was found to be 220 mm of water. Despite oxygen and Digalen therapy, the patient died on the 22nd hospital day.

The discharge diagnoses included *S. suis* septicemia, *S. suis* endocarditis (?), rheumatic heart disease, inactive, with aortic stenosis, and bronchopneumonia.

**Autopsy.** A postmortem examination, limited to the neck, chest and abdomen, was performed on September 27, 1940, 4 hours after death. The pathological diagnoses included septicemia due to *S. suis*, subacute bacterial endocarditis of the mitral valve caused by *S. suis*, acute bronchopneumonia, pulmonary infarction (recent), focal hemorrhage and necrosis of liver, embolic nephritis, acute splenitis, rheumatic heart disease, myocardial fibrosis, stenosis and insufficiency of mitral and aortic valves, cardiac hypertrophy and dilatation, generalized arteriosclerosis, generalized congestion, pulmonary edema, hydropericardium, hydrothorax, dependent edema, pulmonary emphysema and atelectasis, and pulmonary infarction (old).

The heart weighed 560 gm. Its valve measurements were tricuspid, 10 cm, pulmonary, 7.5 cm, mitral, 5 cm, and aortic, 5 cm. The myocardium of the left ventricle measured 2.5 cm in thickness, and that of the right ventricle 0.8 cm. The left ventricle was contracted,

and the left atrium, right ventricle and right atrium were dilated. The tricuspid and pulmonary valves were not remarkable. The mitral valve admitted only the little



FIGURE 2.

finger, and its cusps were markedly thickened. A large, soft, reddish vegetation measuring 1.5 by 1 by 0.5 cm. was attached to this portion of the posterior cusp

lar surface of the anterior cusp. The aortic valve had rigid, thickened, roughened leaflets obstructing the lumen of the valve. Marked calcification was present in the aortic ring and extended upward into the leaflets. No gross vegetations were noted. The endocardium of the left atrium was somewhat thickened. The papillary muscles were hypertrophic, and the myocardium was pale red and markedly friable. The openings of the coronary arteries were somewhat narrowed by the marked arteriosclerotic processes in the sinuses of Valsalva. The coronary arteries were moderately tortuous, and their intima displayed numerous yellowish plaques.

On microscopic examination, the myocardium revealed a few small areas of fibrosis and scattered foci of cellular infiltration composed of lymphocytes, plasma cells, monocytes and polymorphonuclear leukocytes. A number of small recent hemorrhages were present without appreciable cellular response. The mural endocardium in one section was markedly thickened, consisting of hyaline connective tissue, with some infiltration of lymphocytes and plasma cells. Beneath the endocardium was a fairly wide zone of granulation tissue infiltrated with lymphocytes and polymorphonuclear leukocytes. The mitral valve revealed fibrosis, newly formed blood vessels and infiltration with polymorphonuclear leukocytes, lymphocytes, plasma cells and monocytes. Its atrial surface was covered by a large thrombus of fibrin enclosing cellular debris, red and white blood cells, and myriads of small gram-negative bacilli in large clusters (Fig. 4). The tissue immediately underlying the thrombus showed marked leukocytic infiltration and some fibroblastic proliferation.

Cultures taken during the post-mortem examination from the heart's blood, spleen and mitral vegetation were positive for *S. suispestifer* (European type).

#### CLINICAL FEATURES IN SUIPESTIFER ENDOCARDITIS

Except for the presence of bacterial endocarditis, the post-mortem findings in our case were com-

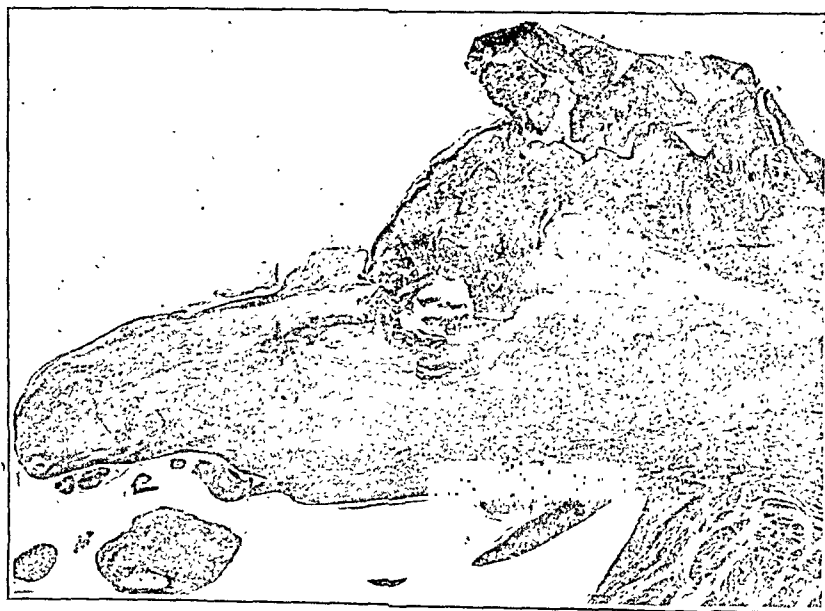


FIGURE 3.

(Figs. 2 and 3). Tiny, granular, friable vegetations were present along the entire line of closure of the mitral valve. The chordae tendineae were thickened and shortened. Plaques of calcified material were present on the ventricu-

patible with those usually found in cases of *suipestifer* bacteremia. The pathology is that of a severe infection and frequently includes bronchopneu-

monia, acute splenitis, focal necrosis of the liver and petechial hemorrhages. Pyarthrosis and osteomyelitis are not infrequent, and meningitis, pericarditis, cystitis, pyelonephritis and abscesses

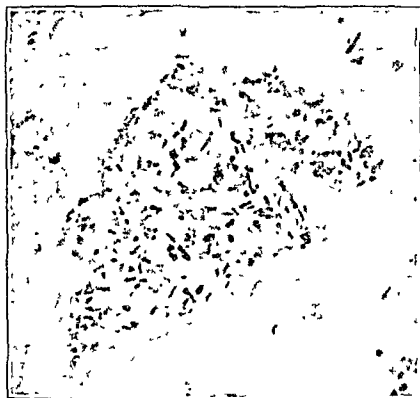


FIGURE 4.

in various parts of the body are found occasionally. To the list of unusual findings, bacterial endocarditis must be added.

The salient features of the 4 proved cases of

no case was the spleen palpable. Fever was high and was associated with chills in all, and leukocytosis, an unusual finding in uncomplicated suispestifer bacteremia, occurred in all the cases. Changing murmurs were noted in 3 patients. Positive blood cultures were readily obtained, and in the only case in which it was mentioned, the agglutination titer was high. Chemotherapy with the sulfonamide drugs was attempted in 3 of the 4 cases, with no evidence that it had an appreciable effect on the course of the disease.

Thus, endocarditis due to *S. suispestifer* may occur and should be suspected whenever changing murmurs, leukocytosis and embolic phenomena are associated with a bacteremia due to this organism.

#### OTHER CASES OF SUIPESTIFER INFECTION IN BOSTON

The appearance of this case of suispestifer endocarditis prompted a review of other cases of suispestifer infection seen in clinics cooperating with the Peter Bent Brigham Hospital.

#### *Suispestifer* Infection in Children\*

Six cases are reported from the Children's Hospital of Boston. These were all due to the European type of *S. suispestifer*. The fact that they are all fairly recent is probably due to more ac-

TABLE 1. Comparison of Four Cases of *Suispestifer* Endocarditis.

AUTHOR	AGE OF PATIENT	SEX	WHITE-CELL COUNT	RED CELL COUNT	TYPE OF ORGANISM	AGGLUTININ TITER	SITE OF LESION	NO OF POSITIVE BLOOD CULTURES	COMMENT
FORSTER <sup>14</sup>	47	M	11 4-33 4	5 0	American	—	Right atrium, left ventricle	3	Patient, a Negro, had had syphilitic aortic insufficiency. Onset of acute and ulcerative endocarditis was insidious. Heart block and increasing systolic murmurs were noted. Hospital course lasted for 6 days.
	31	M	16 0-26 0	5 5-3 2	American	—	Mitral valve	7	Patient had had rheumatic fibrosis of mitral, aortic and tricuspid valves. Onset of acute, ulcerative endocarditis was insidious. Auricular fibrillation and inconstant diastolic murmurs were noted. Hospital course lasted for 21 days. Petechiae and infarcts were noted in spleen, kidney and lungs at autopsy.
READ <sup>15</sup>	49	F	11 7-20 0	5 5-3 9	European	—	Aortic valve	1	Onset of acute endocarditis was postoperative. Aortic systolic and diastolic murmurs were noted. Hospital course lasted for 66 days. Cerebral thrombosis was present.
Gould, Kingsland and Janeway	59	F	13 7-21 0	4 5-2 7	European	H 1 1280 O 1 1280	Mitral valve	5	Patient had had rheumatic mitral and aortic stenosis and insufficiency. Onset of subacute endocarditis was sudden. Premature auricular beats and loud systolic murmurs were noted. Hospital course lasted for 22 days. Infarcts in kidney and lungs were found at autopsy.

bacterial endocarditis due to *S. suispestifer* are summarized in Table 1. In 3 cases, the endocarditis was superimposed on a valve already damaged, twice by rheumatic infection, and once by syphilis. Embolic phenomena were noted in 3 cases—in the skin, spleen, lungs, kidneys and brain. Clubbing of the fingers was absent. In

curate bacteriologic classification than to an increased incidence of the disease.

CASE 2. J. V. (C. H. 178921), a 6-year-old boy, was admitted to the hospital on February 5, 1934, because of a 2-day episode of fever, vomiting and cough productive of

\*We are indebted to the late Dr. Kenneth Blackfan, former physician in chief of the Children's Hospital for permission to report Cases 2, 3, 4, 5, 6, 7 and 11 from the Children's and Infants' hospitals.

blood-streaked sputum. Physical examination revealed an acutely ill boy with numerous ecchymoses on the legs, inflamed tonsillar pillars, pharyngitis, signs of consolidation in the lower portion of the right upper lobe of the lungs and a palpable spleen. The white-cell count was 17,400, and the red-cell count was 4,550,000. A blood culture taken on the day of entry was positive for *S. suispestifer* (European type). The temperature rose to 106°F. on the 2nd day, and then gradually declined until it became normal on the 7th hospital day. During the first week, 2 stool cultures were positive for *Shigella paradysenteriae* (Sonne). The patient was therefore kept in the hospital for 23 days, to obtain a sufficient number of negative stool cultures. One month after discharge, the agglutination titer was 1:320 for the suispestifer H antigen, and 1:640 for the O antigen.

CASE 3. D. G. (C. H. 189434), a 4-month-old boy, was admitted to the hospital on February 15, 1935, because of fever and diarrhea of 2 days' duration. Physical examination revealed a febrile, restless infant with pharyngitis and an inflamed left tonsil. The white-cell count was 15,000, and the red-cell count was 5,050,000. Several stool cultures were positive for *S. suispestifer* (European type), but blood cultures were negative. During the first few days, the patient had numerous loose greenish stools and ran a fever varying from 101 to 102.8°F. The temperature became normal on the 11th hospital day. On the 15th day, the spleen became palpable, but he was in such good condition that he was discharged 2 days later.

CASE 4. T. W. (C. H. 190092), a 9-year-old boy, entered the hospital on March 18, 1935, because of abdominal pain, fever and delirium of 5 days' duration. Physical examination revealed pharyngitis, a palpable spleen and slurred speech. The white-cell count was 4400, and the

CASE 6. B. E. (C. H. 207904), a 2-year-old girl, entered the hospital on June 11, 1938, because of fever, marked sweating, vomiting and diarrhea of 24 hours' duration. Physical examination revealed a drowsy, apathetic, febrile child. The white-cell count was 6000, and the red-cell count was 4,800,000. A blood culture was positive for *S. suispestifer* (European type). The patient ran a high fever and leukopenia for the first 2 days, but the diarrhea promptly subsided. On the 3rd day, the temperature became normal, and the patient was no longer apathetic. She was discharged on the 10th day after three properly spaced stool cultures were reported negative.

CASE 7. R. D. (C. H. 209725), a 2-year-old boy, was admitted to the hospital on June 10, 1939, because of fever and convulsions of 24 hours' duration. Physical examination revealed pharyngitis, rapid breathing and signs of consolidation in the right axilla. The white-cell count was 9600, and the red-cell count was 3,500,000. Two blood cultures were positive for *S. suispestifer* (European type). A lumbar puncture was negative. On the 1st day, the temperature reached a peak of 105°F. It gradually declined until it became normal at the end of the 2nd week. On the 5th hospital day, the liver and spleen became palpable. The patient was discharged on the 21st day.

These cases of suispestifer infection in children were all sporadic. The clinical picture was that of an acute infectious disease, which ran a febrile course of three to fifteen days. The age of the patients varied from four months to nine years, and with one exception all were males. Two cases had acute gastroenteritis with diarrhea. Pharyngitis

TABLE 2. *Suispestifer* Infection in Children.

CASE No.	AGE yr.	SEX	DURATION OF FEVER days	PHARYNGITIS	PNEUMONIA	SPLENO-MEGALY	VOMIT-ING	DIAR-RHEA	WHITE-CELL COUNT × 10 <sup>3</sup>	RED-CELL COUNT × 10 <sup>6</sup>	BLOOD CULTURE	STOOL CULTURE
2	6	M	8	+	+	+	+	—	17.4	4.6	+	—
3	1/3	M	12	+	—	—	—	+	17.8	5.1	—	+
4	9	M	12	+	—	+	—	—	4.4	5.9	+	—
5	6	M	10	—	—	—	—	—	5.4	4.5	+	—
6	2	F	3	—	—	—	+	+	6.0	4.8	+	—
7	2	M	15	+	+	+	—	—	9.6	3.5	+	—

red-cell count was 5,900,000. A lumbar puncture revealed normal spinal fluid. Blood cultures were positive for *S. suispestifer* (European type). The temperature ran from 99 to 100°F. for the 1st week. It then became normal, the patient's irritability subsided, and the spleen was no longer palpable. Before discharge on the 15th day, the agglutination titer was 1:320 for both H and O antigens.

CASE 5. A. L. (C. H. 183420), a 6-year-old boy who had been treated in the Out-Patient Department for a meatal stricture, was admitted to the hospital on September 30, 1935, because of fever, anorexia and difficulty in passing urine. These symptoms began a week before entry and had gradually increased in severity. Physical examination was negative except for fever and a reddened glans with 2 meatal orifices. The white-cell count was 5400, and the red-cell count was 4,530,000. A blood culture was positive for *S. suispestifer* (European type). Both fever and urinary difficulty subsided by the 3rd day, and on the 7th day the patient was discharged.

was found in 4 patients, a palpable spleen in 3, and signs of pneumonia in 2. Only 2 patients had a definite leukocytosis. Of these, one had pneumonia and the other had acute gastroenteritis. Five had positive blood cultures; the one exception was a four-month-old child who had a positive stool culture. These data are summarized in Table 2.

*Suispestifer* Infection Complicating Parturition

Two cases of *S. suispestifer* infection occurred recently in women at the Boston Lying-in Hospital. In each case, the infection was due to the European type of the organism, and its source was unknown. Both newborn infants acquired the infection. One developed coryza, with a positive stool culture, and recovered; the other devel-

oped positive blood, spinal fluid and stool cultures, and died

CASE 8 H T (B L H 29220), a 21 year-old primipara, was admitted to the hospital on March 28, 1940, because of sharp pain in the right flank, radiating down the right thigh to the calf, of 24 hours duration. Prior to admission, she had treated herself with local application of hot water bottles to the right flank and had suffered

more small blood transfusions, and the temperature fell to normal on the 10th hospital day, she made a rapid convalescence. On April 4, she began to complain of severe pain over the right sacroiliac region. On April 20, x-ray films showed slightly diminished radiance and roughening of the articular surface at the inferior border of the right sacroiliac joint. This pain disappeared after 2 or 3 weeks. Agglutination tests for *S. suispestifer* were positive to serum dilutions of 1:80 and 1:320 on April 1,

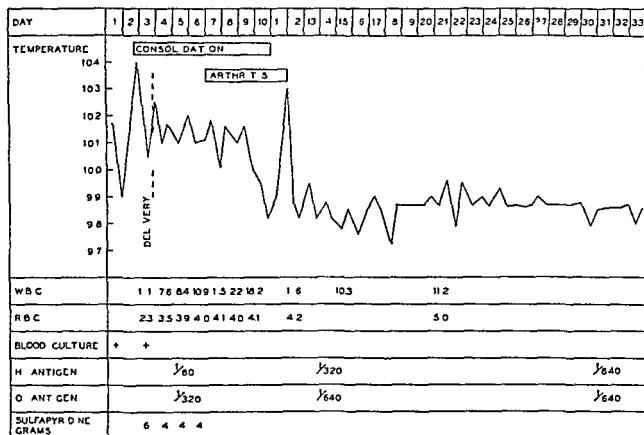


FIGURE 5 Clinical Course in Case 8

second-degree burns. On admission, the temperature was 100.6°F, the pulse 86, the respirations 20, and the blood pressure 104/58. The patient seemed acutely ill, but tenderness in the right costovertebral angle was the only positive physical finding.

The urine contained 3 or 4 white blood cells per high power field in the centrifuged sediment of a catheterized specimen. The hemoglobin was 40 per cent (Sahli), the red cell count was 2,340,000, and the white cell count 11,100. An x-ray film of the kidney region showed no evidence of stone. There was a total blood protein of 5.51 gm, an albumin of 2.98 gm, a globulin of 2.08 gm, and a nonprotein nitrogen of 34 mg per 100 cc. Culture of the urine gave a growth of *Staphylococcus aureus* and hemolytic streptococcus.

During the next 2 days, the temperature rose to 104°F, and the patient experienced five chills during this period (Fig. 5). Blood cultures taken on March 28 and March 30 were positive for *S. suispestifer* (European type). Because of anemia, the patient was given a blood transfusion. On March 30, she went into labor and delivered a baby girl without particular difficulty. Because of persistent fever and signs in the left chest, an x-ray film was taken and interpreted as showing consolidation of the left lower lobe due either to pneumonia or more probably to pulmonary edema resulting from acute cardiac decompensation. Sulfapyridine was administered, and 18 gm was given during the next 4 days without any demonstrable effect on the disease. Several attempts to isolate *S. suispestifer*, streptococci and pneumococci from the sputum were unsuccessful. The patient was given four

of 1:320 and 1:640 on April 10 and of 1:640 and 1:640 on April 27 for the H and O antigens, respectively.

In a follow-up visit on August 15, the patient reported that she had been in good health since her discharge on April 29. The sacroiliac arthritis had not troubled her, and an x-ray film taken at that time showed definite narrowing of the joint and reaction in the bones on either side of the joint, apparently the end result of an inflammatory process. On April 16, 1941, O agglutination of *S. suispestifer* was negative, and H agglutination positive to a serum dilution of 1:160.

CASE 9 Baby T (B L H 29220) was born on March 30, 1940, to the patient in Case 8 by a normal delivery. During the 1st week of life, the baby appeared ill, with poor color, cry and activity and finally developed coryza and a fever reaching 100°F. A stool culture on the 20th hospital day gave a light growth of *S. suispestifer* (European type). Blood taken at the time of discharge on April 29 gave a positive agglutination for *S. suispestifer*, but all blood cultures were negative. A year later, the baby was seen and found to have normal weight and development.

CASE 10 T C (B L H 29171), a 23-year-old para III, who had lost her second child during an attack of eclampsia, was admitted to the hospital on April 13, 1940, 24 hours after delivery on the district service. During pregnancy, the patient was quite anemic. Delivery was by breech extraction with forceps. Delivery of the after-coming head. During this process, the patient lost 300 cc of blood. On the following day, the temperature rose

progressively to 103°F., with a pulse of 150, and hospitalization was therefore advised.

On admission, the patient appeared extremely pale and acutely ill. The temperature was 105°F., the pulse 136, and the respirations 30. Physical examination was otherwise negative.

The urine contained many gram-negative motile rods and 4 or 5 white blood cells per high-power field in the sediment. Examination of the blood showed a red-cell count of 1,770,000 with a hemoglobin of 30 per cent (Sahli), and a white-cell count of 7900. The stained blood smear showed marked variation in the size and shape of the red blood cells, and two nucleated red blood cells were noted. The total blood protein was 5.37 gm. per 100 cc. Cultures of the urine were positive for colon bacilli on three occasions. Two blood cultures were negative, but two out of eight stool cultures showed *S. suispestifer*. Agglutination tests with typhoid bacilli, paratyphoid A and B. bacilli, and *Brucella abortus* were negative, but on April 26 were positive for the H and O antigens of *S. suispestifer* (European type) to a serum dilution of 1:80. Agglutination of a strain of *Escherichia coli* from the stool was very slight.

The patient was given daily transfusions of 500 cc. of citrated blood for the first 6 days, and 1 cc. of concentrated liver extract daily from April 19 to April 23. The temperature, pulse and respirations fell gradually to normal by April 22. At discharge on May 7, the hemoglobin had risen to 84 per cent, and the white-cell count was 7500. Throughout the hospital course, the white-cell count fluctuated between 7900 and 2400.

The patient was seen again on April 16, 1941, when she stated that she had been in excellent health since a subtotal thyroidectomy in January, 1941, performed to relieve hyperthyroidism, which had developed soon after the termination of her pregnancy. At this time, no agglutinins for either the H or O antigen of *S. suispestifer* were detected in her blood.

CASE 11. Baby C. (B. L. H. 23915), a male infant, was born at term on April 12, 1940, to the patient in Case 10 by breech extraction with forceps delivery of the head. The birth weight was 5 pounds, 6 ounces. At 24 hours, the patient was admitted to the Boston Lying-in Hospital with his mother, who was suffering from acute pyelonephritis due to *Esch. coli* and who was later found to harbor *S. suispestifer* in her intestinal tract. For 9 days, the baby appeared well, except for the persistence of jaundice and an episode on the 9th day when the temperature fell to 95°F. On April 22, the temperature rose to 100.8°F., and the patient appeared feeble, apathetic and hypoactive. The extremities were cold and cyanotic, the mucous membranes were pale, and the abdomen was distended. On April 23, the red-cell count was 4,400,000 with a hemoglobin of 75 per cent, and the white-cell count was 14,400. A blood culture was found to be positive for *S. suispestifer* (European type). Because of this infection, the patient was transferred on April 26 to the Infants' Hospital.

On admission, the baby was found to be poorly nourished and poorly developed, apathetic, jaundiced and slightly hyperpneic. The mucous membranes were pale, the abdomen was distended, and the spleen, kidneys and liver were palpable.

The urine sediment contained a few white blood cells and many granular casts per high-power field. The red-cell count was 3,300,000 with a hemoglobin of 80 per cent, and the white-cell count was 21,200. The blood Hinton reaction was negative, the icteric index 90, and the non-

protein nitrogen 58 mg. per 100 cc. Lumbar puncture showed yellowish spinal fluid with a +++ test for globulin, normal sugar, a red-cell count varying from 450 to 5400, and a white-cell count varying from 12 to 92. The last included polymorphonuclear and mononuclear cells. Cultures of the spinal fluid, blood and stools were all positive for *S. suispestifer* (European type), but no agglutinins were found in the blood.

During the 7 days that the infant was at the Infants' Hospital, the temperature was constantly subnormal. Because of recurrent episodes of cessation of respiration, intracranial damage was suspected, and lumbar punctures were performed. The baby was given intravenous glucose and small transfusions, 10 gr. of sulfanilamide for the first 2 days and 63 gr. of sulfathiazole for the next 4 days. Despite all therapy, the patient died May 5, on the 21st day of life. Permission for an autopsy was not granted. The discharge diagnoses were *S. suispestifer* bacteremia and birth injury of the brain, with subarachnoid hemorrhage.

### Summary of Cases

Two other cases of adult infections in Boston were reported in 1936 by Walker, Weiss and Nye.<sup>10</sup> Unlike the cases presented in this paper, these infections were due to the American type of *S. suispestifer*. In one case, a left subdiaphragmatic abscess developed in a twenty-three-year-old salesman who previously had experienced a severe illness characterized by fever, chills and diarrhea. The organism was cultured from the abscess when it was drained at operation. In the second case, a forty-year-old Negress had a cholecystectomy for chronic cholecystitis, and the organism was cultured from the gall bladder at operation.

To these cases, we now may add 11 more cases of sporadic infection due to the European type of *S. suispestifer*—6 cases in children, 2 in newborn infants, 2 in parturient women and 1 in an elderly woman. In this group, 2 deaths occurred—one in a newborn infant, who developed both bacteremia and meningitis, and the other in the elderly woman, who developed bacterial endocarditis. Since the ages ranged from the newborn period to fifty-eight years, there appears to be universal susceptibility to infection of this type. All the patients had high fever, ranging in duration from eight to thirty-eight days. Eight patients had positive blood cultures; the other 3 had positive stool cultures. The patient with bacterial endocarditis had positive stool and urine cultures, in addition to positive blood cultures. The composite clinical picture included chills and fever, coryza and pharyngitis, pneumonia, splenomegaly, abdominal pain, vomiting, diarrhea, arthritis, meningitis and bacterial endocarditis. In uncomplicated bacteremia, the white-cell count tended to remain low, but once localization of the infection occurred, leukocytosis usually developed.

## LABORATORY DIAGNOSIS OF SUIPESTIFER INFECTIONS

The diagnosis of infection due to *S. suipestifer* is made by isolation of the organisms, which can most frequently be done by blood culture and less frequently by stool or urine culture. Once isolated, these organisms are readily identified as members of the paratyphoid group by their morphology (gram negative bacilli), motility, fermentation of dextrose, with the production of gas, and inability to ferment lactose.

Further identification depends on the use of special tests, both fermentative and serologic. *S. suipestifer* is distinguished from all the other *Salmonella* organisms by its inability to ferment arab

of agglutination tests in this large group of morphologically similar organisms have been enormously enhanced by the work of White and of Kauffmann,<sup>17</sup> whose painstaking antigenic analyses carried out with carefully absorbed serums have resulted in the so called "Kauffmann-White scheme of classification."

Weil and Felix<sup>18</sup> first introduced the terms "H" and "O" as applied to motile and nonmotile variants of a culture, H standing for *Hauch* (flagella), O for *ohne Hauch* (without flagella). H agglutinins are antibodies to the antigens of the flagella of the bacteria, and their union with the flagella results in the formation of loose clumps

TABLE 3 Classification of the Commoner *Salmonella* Organisms\*

SALMONELLA GROUP	ORGANISM		SOMATIC ANTIGENS		FLAGELLAR SPECIFIC PHASE	ANTIGENS GROUP PHASE
	OFFICIAL NAME	OTHER NAME OR NAMES	MAJOR	MINOR		
A	<i>S. paratyphi</i>	Paratyphoid A bacillus	I	II	a	—
	<i>S. species</i> (Newcastle or Senftenberg type)	Newcastle B bacillus	I	III	gs	—
P	<i>S. schottmuelleri</i>	Paratyphoid B bacillus	IV XII	V	b	1 2
	<i>S. typhi murium</i>	Motile typhoid bacillus <i>Bact. aertrycke</i> B. <i>festus cat. de</i>	IV XII	X	i	1 2 3
C	<i>S. hirschfeldii</i>	Paratyphoid C bacillus	VI	XII	c	1 4 5
	<i>S. typhi</i> (Eastern type)	<i>S. typhi</i> (Eastern type)	VI	XII	c	1 3 4 5
	<i>S. cholerae suis</i>	<i>S. typhi</i> (American type)	VI	VII	c	1 3 4 5
	<i>S. cholerae suis</i> (Kunzeendorf type)	<i>S. typhi</i> (European type)	VI	VII	—	1 3 4 5
D	<i>S. enteritidis</i>	Enteritidis bacillus	IX XII	—	gm	—
	<i>S. species</i> (London type)	<i>Salmonella</i> Type L	III X	—	iv	1 4 6
F	<i>S. species</i> (Aberdeen type)	<i>Bact. aberdeen</i>	XI	—	i	1 7 3
G	<i>S. species</i> (Poona type)	<i>Bact. poona</i>	XIII	—	z	1 4 6
I	<i>S. species</i> (Hittingfoss type)		XVI	—	b	—

\*There are many other organisms in Groups B, C and D a total of 68 being listed in the last edition of Bergey's *Determinative Bacteriology*.

†The typhoid bacillus (*Escherichia typhosa*) although not strictly a *Salmonella* organism is antigenically a member of Group D with an antigen formula 9 12 d. It is always in the specific phase.

inose. Its inability to ferment inositol and trehalose may be used as confirmatory evidence. It is distinguished in this manner from *S. hirschfeldii* (paratyphoid C bacillus, also known as the Eastern type of *S. suipestifer*) which ferments arabinose, usually trehalose, but not inositol. The American and European types, known as *S. suipestifer* and *S. suipestifer var. kunzeendorf* respectively, are separated on the basis of hydrogen sulfide production, which can best be tested by the use of Kligler's iron agar. The European type produces hydrogen sulfide, which gives black colonies on Kligler's agar, whereas the American type does not.

Although these biochemical reactions justly deserve an important place in the classification of the gram negative bacilli, most laboratories make use of agglutination tests with stock antisera to confirm the tentative identification made by sugar fermentations. The accuracy and specificity

and prompt immobilization of the motile bacteria. Thus, H agglutination becomes readily visible within two hours at 55°C as large, coarse flocules, or microscopically is visible almost instantly as an immobilization of the bacteria with the formation of loosely tangled groups of organisms. On the other hand, the O or somatic agglutinins are directed to the antigens of the cell bodies. If the organisms are motile, or if the flagella are preserved as in a formalinized suspension, O agglutination does not occur, because H agglutination occurs first. However, if the flagella are removed by chemical treatment, or by the production of a nonmotile variant, O agglutination can be demonstrated. Since the bacterial bodies are sensitized, tight packing of the bacteria takes place as agglutination proceeds. Consequently, the clumps formed are small, and it takes six to twelve hours at 55°C for macroscopic agglutination to occur. H suspensions are either live mo-



tile cultures or formalinized suspensions. O suspensions are prepared from a nonmotile variant or by treating a culture of a motile organism with 50 per cent alcohol for twenty-four hours, or with a temperature of 100°C. for 15 minutes, either of which procedures destroys the H antigens. H agglutination tests are read after two hours at 55°C. and refrigeration overnight; O agglutination tests are read after six hours at 55°C. and refrigeration overnight.

The Kauffmann-White classification<sup>19, 20</sup> divides the *Salmonella* organisms into eight different groups on the basis of their O or somatic antigens, which are conventionally represented with Roman numerals. The different species within the groups are separated on the basis of their H or flagellar antigens, for which small letters are used, or, in some cases, on the basis of minor O antigens. Unfortunately, many of these organisms can exist in two phases. In the specific phase, an organism possesses flagellar antigens peculiar to itself, but in the group phase the flagellar antigens are common to many other members of the *Salmonella* group. These group H antigens are represented by Arabic numerals. Table 3 gives the antigenic formulas for the commoner members of the *Salmonella* group, arranged according to Kauffmann's scheme, with the various names used for the different species.

It will be noted that *S. suispestifer* (American type) can exist in both group and specific phases, whereas *S. suispestifer* var. *kunzensdorf* (European type) can exist only in the group phase. Thus, when the former is in the group phase, it cannot be distinguished from the latter by agglutination, and the test for hydrogen sulfide production must be used.

When all this is known, it becomes apparent that the use of the agglutination reaction is beset with pitfalls unless one knows what phase the antigens are in and what phase the organism was in when injections were made to produce the diagnostic serum. If only H agglutination is used, mistakes may be frequently made. For example, the antigenic formula for *S. schottmuelleri* (paratyphoid B bacillus) is IV, XII, V : b : 1, 2, and that for *S. typhi murium* is IV, XII, V : i : 1, 2, 3. These two organisms are among the most frequent to be isolated from *Salmonella* infections in this area. If an organism is isolated that seems to belong to the *Salmonella* group, it would probably be tested first in serum made against *S. schottmuelleri*. If the serum were made with organisms in the group phase, it would contain antibodies to the group flagellar antigens 1 and 2. If the unknown organism happened to be *S. suispestifer* var. *kun-*

*zensdorf*, which is always in the group phase, it would agglutinate to a marked extent, because its flagellar antigens are 1, 3, 4 and 5, the first of which it shares with *S. schottmuelleri*. This confusion can be straightened out by fermentation tests with arabinose and trehalose, both of which are fermented by *S. schottmuelleri* and not by *S. suispestifer*. Furthermore, if the unknown culture is heated to boiling for half an hour to destroy the H antigens, it can then be retested as an O suspension. Under these conditions, it will agglutinate only in a serum made against a member of Group C, which contains somatic antigens VI and VII. This is a very useful procedure, which we have had to use in completing the identification of the organisms isolated from some of the cases reported in this paper, since they gave H agglutination in both our stock *suispestifer* and paratyphoid B antisera.\*

It is therefore quite obvious that the final identification of many *Salmonella* strains is beyond the scope of the ordinary hospital laboratory. On the other hand, the *Salmonella* Center† in New York City is equipped for antigenic analysis, and strains may be sent there for identification. Although this procedure seems like a rather academic matter, it is of great epidemiologic interest to identify as many strains as possible, so that data on the distribution and mode of spread of these organisms may be obtained.

Next to a blood culture, the agglutination test is most useful in making a diagnosis of this type of infection, and should be used in cases of obscure fever. In Harvey's<sup>3</sup> series of cases, 88 per cent gave positive agglutination reactions by the fourth week of the disease. It is essential to get serum from a patient early in the disease, so that it may serve as a control for later tests, which may show positive reactions.

To ascertain the value of the agglutination test in the diagnosis of *S. suispestifer* infection in the Boston area, we have studied a considerable number of serums. We have used both H and O antigens, the former prepared by formalinizing an eighteen-hour culture of the European type of *S. suispestifer* (group phase), and the latter by a twenty-four-hour treatment of the culture with 50 per cent alcohol. From what has already been said, a positive O agglutination would be expected following any infection caused by a member of Group C, and a positive H agglutination would occur after infection with any organism of the

\*Subsequent antigenic analysis of the paratyphoid B strain from which our stock antiserum was made has shown that it has organisms in both the group and the specific phases, which accounts for the lack of specificity of our paratyphoid B antiserum and antigen.

†The *Salmonella* Center, Beth Israel Hospital, New York City, corroborated our bacteriologic diagnosis in Cases 1, 8 and 9.

Salmonella group that happened to be in the group phase and to contain any of the flagellar antigens 1, 3, 4 and 5. In typhoid infection, it is believed that O agglutination is of more significance than H agglutination, since the latter may be increased as a result of prophylactic inoculation, whereas the titer of the former rises less with immunization but may go very high with infection.

We studied a number of normal serums to determine whether agglutinins for *S. supestifer* were present. A similar study was made with serums taken from patients six weeks after immunization with typhoid paratyphoid B vaccine. Since none of these serums showed any significant degree

sistence of agglutinins following infection with this organism. We were able to obtain serums from 6 patients who had had their infections from one to six years previously.

The data on these cases and on all the agglutination tests are summarized in Tables 4 and 5.

The Widal test, as ordinarily done, consists in testing an unknown serum against suspensions of typhoid and paratyphoid A and B bacilli. It is much more sensible to adapt it to the needs of the locality. In the Boston area, the commonest Salmonella infections are due to *S. schottmuelleri* (*Bact. paratyphosum B*), *S. typhi murium* and *S. supestifer var. kunzendorf*, so that suspensions of these organisms should be used in the Widal test. The inclusion of a suspension of *S. supestifer var. kunzendorf* has the added advantage of being in the group phase and, thus, of being able to detect antibodies to the group phase of almost all members of the Salmonella group. The other suspensions should be in the specific phase. We include a single O suspension, usually prepared from typhoid bacilli, in our Widal test, since there is some evidence that O antibodies are less specific in man than in rabbits. Moreover, O antibodies may occasionally develop in typhoid fever without H antibodies.

#### SUMMARY AND CONCLUSIONS

From a survey of the literature, it is apparent that *Salmonella supestifer* infection occurs in epidemic

TABLE 4 Results of Agglutination Tests with Serums from Normal Subjects and Those Immunized with Typhoid Paratyphoid B Vaccine

SERUM	NUMBER OF SUBJECTS	SERUM DILUTION TITERS			
		TY PHOID II	PARA TYPHOID B II	SUI PESTIFER II	SUI PESTIFER O
Normal subjects	34	—	—	0	0
Immunized subjects	4	1 160	1 80	1 10	0

of agglutination with either the H or O antigen, it must be assumed that a positive agglutination test for *S. supestifer* has considerable significance in this locality. However, since our patients with supestifer infections developed equally high titers of H agglutinins for *S. supestifer* suspensions and for our stock suspension of *S. schottmuelleri* (para-

TABLE 5 Persistence of Agglutinins after Supestifer Infection

CASE NO	PERIOD AFTER INITIAL INFECTION	AGGLUTININS	RESULTS IN VARIOUS SERUM DILUTIONS						ORIGINAL TITER
			1 10	1 20	1 40	1 80	1 160	1 320	
3*									
2	6	H	+++	++	+	0	0	0	1 320
		O	+	0	0	0	0	0	1 640
4	5	H	+++++	+++++	+++	++	+	±	1 320
		O	+++++	+++++	+++	++	+	0	1 320
5	5	H	+++	+++	+	0	0	0	—
		O	0	0	0	0	0	0	—
7	1½	H	+++	+++	+++	++	+	0	—
		O	+	+	+	±	0	0	—
8	1	H	+++	+++	+++	++	±	0	1 640
		O	0	0	0	0	0	0	1 640
10	1	H	+	0	0	0	0	0	1 80
		O	0	0	0	0	0	0	1 80

+ = minimal positive agglutination  
++++ = maximal positive agglutination

typhoid B bacillus),\* H agglutination is not specific. But when titers for both H and O agglutinins are found to be elevated, we consider it diagnostic of infection with *S. supestifer* or a related organism in Group C.

Another important question concerns the per-

\*See first footnote on page 136

form as acute food poisoning, with low mortality, and in endemic form at any age, with a considerable mortality, because it often complicates some debilitating disease. These latter cases are characterized by fever, frequently leukopenia, bacteremia and a tendency for the infection to localize in the bones, joints or lungs.

Eleven cases of sporadic infection occurring in the vicinity of Boston during the past six years are reported.

The clinical course and post-mortem findings in a fatal case of bacterial endocarditis due to *S. supestifer* in a fifty-eight-year-old woman with rheumatic valvular disease are described.

The bacteriologic diagnosis of this infection is discussed. A positive blood culture most frequently reveals the diagnosis, occasionally a positive stool or urine culture. *S. supestifer* is identified as a paratyphoid bacillus that does not ferment arabinose.

The significance of the agglutination reaction in this infection is discussed. Agglutinins for *S. supestifer* were not found in normal serums, nor in the serums of patients immunized with typhoid-paratyphoid B vaccine. High agglutination titers were found in the serums of most patients with supestifer infection, and these persisted for periods varying from a few months to six years after infection in a small group of cases.

The importance of using standard antigens and properly prepared antiserums in the identification of the various *Salmonella* types is pointed out.

#### REFERENCES

- 1 Longcope, W. T. Paracolon infections, together with the report of a fatal case with autopsy. *Am J M Sc* 124:209-217, 1902

- 2 MacAdam, W. An account of an infection in Mesopotamia due to bacillus of the Gaertner paratyphoid group. *Lancet* 2:189-193, 1919
- 3 Harvey, A. M. *Salmonella supestifer* infection in human beings: review of the literature and report of twenty one new cases. *Arch Int Med* 59:118-135, 1937.
- 4 Bullock, J. G. M. *Bacillus supestifer* (hog cholera) infection of the lung. *M Clin North America* 12:691-694, 1928
- 5 Cohen, L., Fink, H., and Gray, J. *Salmonella supestifer* bacteremia with pericarditis, pneumonitis and pleural effusion (report of a case). *J A M A* 107:331-333, 1936
- 6 Kuttner, A. G., and Zepp, H. D. Paratyphoid like fever in children due to the *Salmonella supestifer* group. *Bull. Johns Hopkins Hosp* 51:373-387, 1932
- 7 Boycott, J., and McNee, J. W. Human infection with the American hog cholera bacillus a third example in England. *Lancet* 2:741, 1936
- 8 Ravitch, M. M., and Washington, J. A. *Salmonella* septicaemia and meningitis complicating meningococci septicaemia and meningococci meningitis. *J A M A* 109:1122, 1937
- 9 Clifton, W. M., and Werner, N. Infection with *Salmonella supestifer* (hog cholera bacillus) in childhood with report of a case of bilateral subdural abscess ending in recovery. *Am J. Dis Child* 55:553-558, 1938
- 10 Neukirch, P. Über menschliche Erkrankungen durch Bazillen der Glasser Voldagsen Gruppe in der Türkei. *Ztschr. f. Hyg u Infektionskr* 85:103-145, 1918
- 11 Gray, L. A. *Salmonella supestifer* infection in myoma of the uterus. *Bull Johns Hopkins Hosp* 59:231-236, 1936
- 12 TenBroeck, C. L., C. P., and Yu, H. Studies in paratyphoid B bacilli isolated in China. *J Exper Med* 53:307-315, 1931
- 13 Goufey, B. A., and Israel, S. L. *Salmonella supestifer* bacteremia with acute endocarditis. *Arch Int. Med* 53:699-705, 1934
- 14 Forster, D. E. Fetal bacterial endocarditis due to *Salmonella supestifer*. *Am J M Sc* 197:234-240, 1939
- 15 Reid, C. T. Endocarditis caused by *Salmonella supestifer*. *J Infect Dis* 65:263-266, 1939
- 16 Walker, I. J., Weiss, S., and Nye, R. N. *Salmonella supestifer* infection with surgical complications. *New Eng J Med* 214:567-572, 1936
- 17 Kauffmann, F. Die *Salmonella* Gruppe mit besonderer Berücksichtigung der Nahrungsmittelvergifter. *Ergebn d. Hyg, Bak., Immunitätsforsch u exper Therap* 15:219-275, 1934.
- 18 Weil, E., and Felix, A. Weitere Untersuchungen über das Wesen der Fleckfieberagglutination. *Wien. Klin Wchnschr.* 30:1509-1511, 1917
- 19 Topley, W. W. C., and Wilson, G. S. *The Principles of Bacteriology and Immunology*. 2nd edition. 1645 pp. Baltimore: Williams Wood and Company, 1936. Pp 546-572.
- 20 Bergey, D. H., Breed, R. S., Murray, E. G. D., Hitchens, A. P. *Bergey's Manual of Determinative Bacteriology. A key for the identification of organisms of the class schizomycetes*. 5th edition. 1032 pp. Baltimore: Williams and Wilkins Company, 1939. P 456

## THE ACTION OF FURMETHIDE (FURFURYL-TRIMETHYL-AMMONIUM IODIDE) ON THE BLADDER IN PATIENTS WITH URINARY RETENTION FOLLOWING SURGERY ON THE RECTUM\*

### Preliminary Report

JOSEPH H. LIPTON, M.D.,† SAMUEL B. BEASER, M.D.,‡ AND MARK D. ALTSCHULE, M.D.§

BOSTON

A NUMBER of parasymphomimetic drugs, such as Mecholyl and Doryl, are known to cause contraction of the bladder, but untoward side effects limit their clinical use. A new parasymphomimetic drug, Furmethide (furfuryl-trimethyl-ammonium iodide), has been found to have a strong action on the bladder and relatively little effect on the cardiovascular or gastrointestinal system, so that distressing side reactions are not common following its use in the treatment of the atonic bladder. The action of Furmethide

is being studied at present in a wide variety of bladder atonies, including those associated with diabetes, lesions of the spinal cord, postoperative states and trauma to the bladder. Since a complete evaluation of the effectiveness of the drug will require many months, it is considered desirable to call attention to its usefulness by describing its action in one of the syndromes studied, that is, urinary retention following operations on the rectum.

### MATERIAL AND METHODS

All patients, excluding those with prostatic obstruction, subjected to abdominoperineal operations for carcinoma of the rectum during the period of this study were observed. They were placed on constant catheter drainage for ten to fourteen days after operation, or until they were

\*From the Medical Research Laboratories and the Medical, Urologic and Surgical services, Beth Israel Hospital, and the Department of Medicine, Harvard Medical School

This investigation was aided by a grant from Smith, Kline and French Laboratories, Philadelphia

†Resident in urology, Beth Israel Hospital

‡Assistant in medicine, Harvard Medical School, junior visiting physician, Beth Israel Hospital

§Associate in medicine, Harvard Medical School, associate visiting physician, Beth Israel Hospital

ambulatory Intermittent catheterization was employed following removal of the tube. No treatment was given if the volume of residual urine was small. If, however, it was greater than 300 cc, or if the patient could not void spontaneously, treatment with Furmethide was begun. This report is based on the results in 3 consecutive cases. Twelve patients with normal uninfected bladders were used for control studies.

A continuous flow recording cystometer of the type described by Prien<sup>1</sup> was used, previous studies by one of us (J H L) had demonstrated its sensitivity and accuracy. The patient was placed in the recumbent position and, after he had voided, was catheterized, control cystometric measurements were made of vesical pressure during filling, first

TABLE 1 *Average Effect of 5 Mg Furmethide on Cystometric Measurements in 12 Normal Subjects*

OBSERVATION	BEFORE DRUG	AFTER DRUG
Vesical pressure	11-17 cm. water	7-57 cm. water
First desire to void	150 cc	40 cc
Slight discomfort or fullness	400 cc	50 cc
Severe discomfort or fullness	410 cc	55 cc
Maximal voluntary pressure	0 cm. water	80 cm. water
Vesical capacity	410 cc	75 cc

desire to void, slight discomfort or fullness, severe discomfort or fullness, maximal voluntary pressure and vesical capacity. Furmethide was then given

residual urine, cystometric studies showed normal vesical pressure during filling, first desire to void at 400 cc and a vesical capacity of 425 cc. After the administration of 5 mg of Furmethide subcutaneously, a marked increase in vesical pressure during filling occurred (Fig 2), with first desire to void at 40 cc and a vesical capacity of only 50 cc. A second determination yielded similar results. Sweating, lacrimation and salivation occurred. The next day, 4 mg was given subcutaneously, 300 cc of urine was voided spontaneously within 10 minutes, and the residual urine volume was only 75 cc. Voiding of small amounts continued during the day. On June 10, the administration of 30 mg subcutaneously resulted in spontaneous voiding, with a residual urine volume of 20 cc. On the next day, the drug was not given and the residual urine increased to 150 cc. On June 12, the drug was given orally, in doses of 10 mg, twice during the day, the patient voided well and the residual urine volume was only 20 cc. The drug was discontinued on June 14, and at the time of discharge 5 days later, the residual urine volume was still only 50 cc.

CASE 2 A 67-year-old man was subjected to a one stage abdominoperineal resection of an adenocarcinoma of the rectum on March 4, 1941. Constant catheter drainage was continued until March 17, after which intermittent catheterization repeatedly yielded 450 cc of residual urine. Cystometric studies 5 days later showed normal tension, first desire to void at 300 cc, and a vesical capacity of 400 cc (Fig 3). The administration of Doryl subcutaneously from March 18 to 22 did not appreciably affect bladder function, the residual urine volume ranging between 150 and 390 cc. The administration of 5 mg of Furmethide subcutaneously caused a marked increase in vesical pressure during filling, with desire to void at 90 cc and a vesical capacity of 140 cc (Fig 3). On March 23, 3 mg

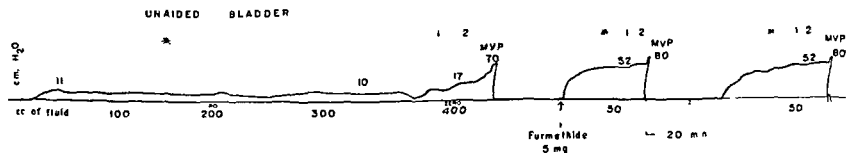


FIGURE 1 *Effect of Furmethide on the Normal Bladder*  
The asterisks indicate the first desire to void

subcutaneously in doses of 3 to 5 mg. Within five minutes, mild salivation, sweating, a feeling of warmth and a desire to void occurred. A second series of cystometric measurements was begun at this time. The effects of the injection of Furmethide on the bladders of the 12 control subjects are summarized in Table 1 and Figure 1.

#### CASE REPORTS

CASE 1 A 64-year-old man was subjected to a one stage abdominoperineal resection of an adenocarcinoma of the rectum on May 24, 1941. The tumor was found to be fixed to the base of the bladder, which was accordingly mobilized extensively and its serosa stripped away. Constant urinary drainage was begun after operation and continued until June 8, after which the patient voided only in small amounts and was found to have 400 cc of

of the drug was given subcutaneously after which the patient voided 350 cc and was found to have only 100 cc of residual urine. On the following 2 days, no drug was given, and 475 cc of residual urine was found repeatedly. Beginning on March 26, the drug was given orally in doses of 10 mg three times a day. Spontaneous voiding was maintained, and the volume of residual urine decreased to 20 cc on March 30. At the time of discharge on April 3, the residual urine was still less than 30 cc.

CASE 3 A 45-year-old man was subjected to a one stage abdominoperineal resection for adenocarcinoma of the rectum on May 23, 1941. Constant catheter drainage was employed until June 6, after which the volume of residual urine ranged between 400 and 900 cc. Cystometric studies on June 13 showed a neurogenic bladder curve, with first desire to void at 800 cc and a vesical capacity of 850 cc. After the administration of 5 mg of Furmethide subcutaneously, there was an increase in vesical pressure during filling with first desire to void at 100 cc and a

vesical capacity of 150 cc. (Fig. 4). On a regime of 5 mg of the drug subcutaneously, twice daily, the volume of residual urine decreased to 150 cc. On June 18, the drug

urine to 40 cc.; withdrawal of the drug resulted in an increase to 250 cc. on September 18, with first desire to void at 325 cc. and a vesical capacity of 500 cc. Since that

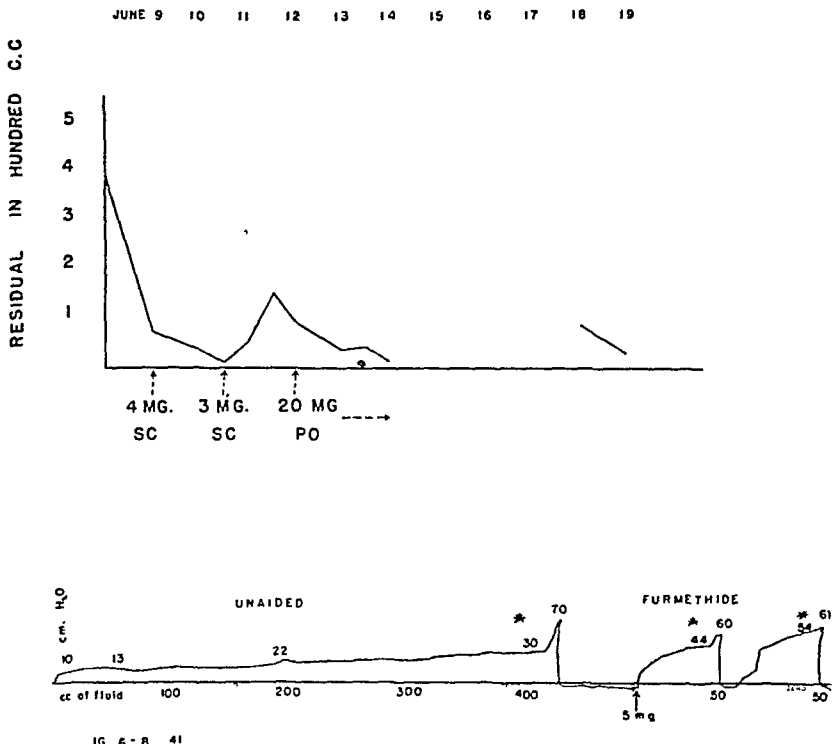


FIGURE 2. Findings in Case 1.

was started orally, in doses of 25 mg. twice daily, and the residual urine volume rapidly decreased to 40 cc. The patient was discharged, with orders to continue that

time, the patient has been taking 10 mg. of Furmethide by mouth twice daily. He empties his bladder almost completely, the stream is full, and he has no urinary symp

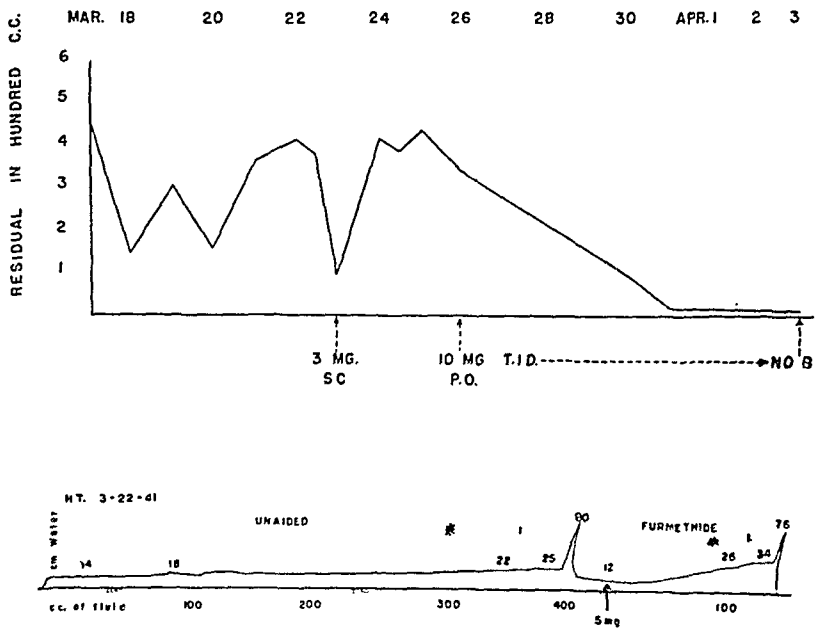


FIGURE 3. Findings in Case 2.

dosage; on July 9, the volume of residual urine was 50 cc., and cystometric studies yielded essentially normal results, with first desire to void at 210 cc. and a vesical capacity of 280 cc. The drug was discontinued, and on July 23 the residual urine volume was 250 cc. Resumption of oral Furmethide therapy reduced the volume of residual

toms. He experiences only mild sweating and a feeling of warmth after taking the drug.

DISCUSSION

The importance of urologic complications following major operations on the rectum has been

stressed by Ewert<sup>2</sup> and by Seaman and Binnig.<sup>3</sup> Ewert found 219 cases of urologic disturbance among 750 cases with operations on the colon, 75 per cent of them in patients after rectal surgery; some of the patients required tidal drainage for periods of one to three months. Seaman and

fore considered. The effective manner in which the administration of Furmethide has been found to control bladder dysfunction following major operations on the rectum is clearly exemplified by the findings in the cases described.

When Furmethide is given in doses of 3 mg.

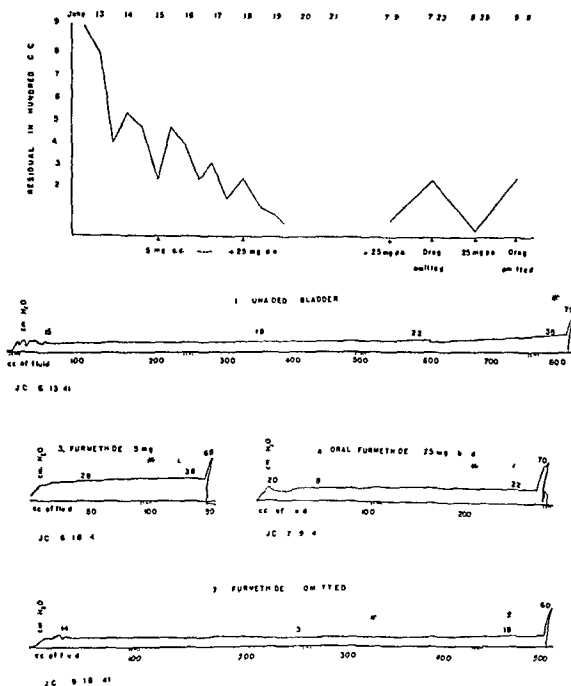


FIGURE 4 Findings in Case 3

Binnig<sup>3</sup> also reported the frequent need for tidal drainage following resection of the rectum and mentioned attempts to control the symptoms by means of the injection of Mecholyl and ergotamine tartrate. A similarly high incidence of urinary complications after abdominoperineal resection has been observed at the Beth Israel Hospital. It was believed that bladder dysfunction after resection of the rectum was probably due to detrusor atony resulting from damage of the parasympathetic nerve supply of the bladder, and that the administration of parasympathomimetic drugs might therefore control the symptoms. The employment of Mecholyl and of Doryl having proved generally unsatisfactory, the clinical uses of Furmethide, previously shown by other authors<sup>4-6</sup> to have somewhat similar pharmacologic effects, was there-

subcutaneously or 10 mg. by mouth, the side reactions consist only in slight sweating and a feeling of warmth. With somewhat larger doses, these symptoms are more marked, and salivation is pronounced. Still larger doses, that is, 10 mg. subcutaneously or 30 mg. by mouth, cause severer discomfort and may also give rise to nausea and vomiting. In all cases studied thus far, however, it has been possible to find a dose of the drug that is effective in its action on the bladder and does not cause significant discomfort because of the side effects.

The chemical similarity of Furmethide to Mecholyl and Doryl is based on the fact that all contain a trimethyl ammonium halide group (Fig. 5). Furmethide differs from the other two pharmacologically in that its action on the heart and lungs

is weaker than that of Mecholyl, its action on the gastrointestinal tract is weaker than that of Doryl, and its action on the bladder is consid-

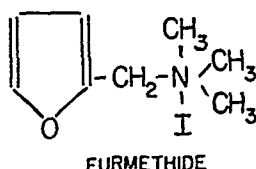
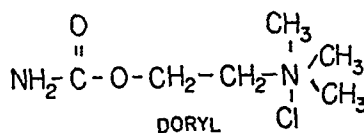
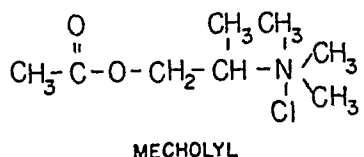


FIGURE 5. Structural Formulas of Mecholyl, Doryl and Furmethide.

erably stronger than both. The advantages of these properties for the control of atony of the bladder are clear.

## SUMMARY AND CONCLUSIONS

The action of Furmethide (furfuryl-trimethylammonium iodide) on the normal bladder and on the bladder that has become atonic after major operations on the rectum is described. Its effect is to increase tone, restoring it in atony to or toward normal. The drug has been used effectively in the control of bladder dysfunction in 3 cases after abdominoperineal resection of carcinoma of the rectum. Although discomfort due to side reactions may be appreciable after administration of large doses of Furmethide, in clinical usage it has been possible to find a dose that is effective in its action on the bladder and does not cause significant discomfort because of the side effects.

## REFERENCES

1. Prien, E. Personal communication.
2. Ewert, E. E. An analysis of the complications following large bowel surgery. *J. Urol.* 46:764-776, 1941.
3. Seaman, J. A., and Binnig, C. Urological complications of cancer of the rectum. *J. Urol.* 46:777-787, 1941.
4. Fellows, E. J., and Livingston, A. E. The pharmacology of certain furfuryl and tetra-hydro-furfuryl ammonium iodides. *J. Pharmacol. & Exper. Therap.* 68:231-246, 1940.
5. Fellows, E. J., and Livingston, A. E. The circulatory action after atropine of certain furfuryl ammonium iodides and of acetyl-beta-methylcholine chloride (mecholyl). *J. Pharmacol. & Exper. Therap.* 71:187-196, 1941.
6. Myerson, A., Rinkel, M., Loman, J., and Dameshek, W. The effect of furfuryl trimethyl ammonium iodide on various autonomic functions in man. *J. Pharmacol. & Exper. Therap.* 68:476-481, 1940.

## PRIMARY ADENOCARCINOMA IN A MECKEL'S DIVERTICULUM

HOLLIS L. ALBRIGHT, M.D.,\* AND JOHN S. SPRAGUE, M.D.†

BOSTON

INCREASING attention is being directed to Meckel's diverticulum, as judged by the reports in the literature of collected rather than single cases. The diverticulum has been estimated to be present in 2 per cent of all adults (Nygaard and Walters,<sup>1</sup> and Skinner and Walters<sup>2</sup>). It is usually observed as an incidental finding either at operation or at post-mortem examination. Symptoms do not usually arise until pathologic changes have taken place in the diverticulum. The complications are frequent, varied and almost always severe, and are of prime clinical importance; they may lead in some cases to an acute surgical emergency, and in others to a belatedly recognized cause of death. Attention is directed here to neoplastic disease of the diverticulum, particularly carcinoma.

Normally, the yolk stalk (omphalomesenteric

duct), which connects the alimentary canal with the yolk sac, becomes closed during the fifth week of fetal life. Failure of this duct to become completely obliterated may lead to any one of four anomalies. If the duct remains entirely open, an intestinal fistula results, with discharge of ileal contents through the umbilicus; this differs from a patent urachus because of the discharge of feces rather than urine. Secondly, if the duct remains open throughout its distal portion, an umbilical fistula results, with active secretion from its glandular lining. Thirdly, if the duct becomes obliterated at both ends but fails to close in the middle, a retention cyst or true enterocystoma forms, requiring surgical removal. Fourthly, if only the distal end closes and the ileal end remains open, a true Meckel's diverticulum results.

There are several distinguishing characteristics of a Meckel's diverticulum. It is usually located from 25 to 100 cm. from the cecum, almost always on the antimesenteric border. According to Reiser,<sup>3</sup> the wall usually lacks the circular mus-

\*Instructor in surgery, Boston University School of Medicine; visiting surgeon, Massachusetts Memorial Hospitals.

†Assistant in surgery, Boston University School of Medicine; second assistant visiting surgeon, Massachusetts Memorial Hospitals.

culature. When all the layers of normal intestine are present, the diverticulum may actively discharge its contents. In the case reported here, the diverticulum was 1 cm. away from the mesenteric border. The neck may vary widely in size, from the usual broad sessile type to the very narrow, as in our patient. A very narrow opening into the ileum may lead to impaction and decomposition of the diverticular contents. This may explain why preoperative x-ray studies with barium fail to disclose the diverticulum.

Histologically, the diverticulum is usually lined with ileal mucosa. In approximately 25 per cent of the cases, however, heterotopic mucosal variations have been observed. Typical mucositis of the gastric or jejunal types and pancreatic tissue are the chief variants seen. Gastric mucosa occurs oftenest at the neck of the diverticulum, and it is thought that the secretion of hydrochloric acid by the mucosal glands disposes to erosion, ulceration and hemorrhage at this site.

Pathologic changes, occurring in 25 to 33 per cent of the cases (Nygaard and Walters<sup>1</sup>), may be described as mechanical, inflammatory, heterotopic and neoplastic. The contents may undergo decomposition, especially if the neck of the diverticulum is narrow. Gangrene and obstruction may result from volvulus or invagination of the diverticulum into the ileum to cause intussusception. Inflammatory changes may predominate, as in idiopathic diverticulitis with regional peritoneal irritation, and in later stages, perforation and diffuse peritonitis. Peptic ulcer arising in aberrant gastric mucosa is the more prominent disturbance associated with heterotopic tissue formation. The ensuing intestinal hemorrhage may be depleting and severe. Neoplastic changes in the diverticulum have been observed in the form of myoma, lipoma, neuroma, papilloma and carcinoid as benign growths, and sarcoma and carcinoma as malignant growths, with and without metastases to the mesenteric nodes.

The greater number of diverticula are uncomplicated, cause no symptoms, and are found incidentally at operation or autopsy; they rarely contain heterotopic tissue. The varied complications give rise to no single, characteristic syndrome. Nevertheless, a revealing, more or less definite symptom complex may be seen in the major types of lesions. Pain, soreness or tenderness is present in approximately 50 per cent of the cases. The pain is usually intermittent, colicky and moderate, and occurs chiefly in the right lower abdomen. The tenderness is often localized to the right or left of the umbilicus.

Symptoms of obstruction have arisen more commonly from intussusception and adhesive bands,

either inflammatory or connecting the diverticulum to the umbilicus, thus obstructing a loop of adjacent bowel. Volvulus is much less common. Over 170 cases of intussusception due to an invaginated Meckel's diverticulum have been collected and reported (Halkins<sup>4</sup> and Greenblatt et al.<sup>5</sup>). In addition, inflammatory lesions may lead to adhesions between the diverticulum and bowel, resulting in obstruction.

The symptomatology of the diverticulitis group simulates that of appendicitis, except that the tenderness has often been localized at or to the left of the umbilicus. Unless the appendix has been previously removed, it may be impossible to differentiate diverticulitis from appendicitis. This will not delay the institution of proper treatment, however, for such a syndrome should lead to early surgical intervention in both situations.

The peptic group<sup>6</sup> may simulate the peptic-ulcer syndrome, the symptoms depending on the presence of ulceration, hemorrhage or perforation, with peritonitis. Intestinal hemorrhage has been found to be the essential finding, and often the only one, of this group. Acute anemia may result. Vague to definite periumbilical pains, often related to meals and associated with past or recurring intestinal hemorrhage, suggest the diagnosis. Not every case of ulceration has hemorrhage, perforation or pain, yet all three may be present.

The chief symptoms arising from an umbilical fistula are soreness, tenderness and a mucopurulent or fecal discharge. The diagnosis rests between a persistent omphalomesenteric duct and patent urachus. If a fecal fistula is present, the latter is more certainly excluded.

Tumors arising in the diverticulum cause indefinite primary symptoms referable to the tumor itself, and more pronounced secondary symptoms arising from superimposed complications. Lower abdominal distress and intermittent, moderately severe, cramplike pain have been found in 50 per cent of the cases. Frequently, the pain may be referred to the epigastrium. The tumor was palpable in 5 of the 20 cases reviewed by Nygaard and Walters<sup>1</sup>. Two of these were revealed by pelvic examination. Mention is made of the tendency for the tumor to slip away from the examining hand. Generally, symptoms and signs depend not so much on the size of the tumor as on the secondary complications, such as bleeding, intussusception, obstruction, perforation and local or diffuse peritonitis. In most of these patients, preoperative x-ray studies of the passage of barium through the small bowel have not been employed because of the signs of an acute inflammatory condition. Consequently, the literature on the positive roentgenologic findings has



been meager. In the less acute cases, however, serial studies of the small bowel—namely, films taken hourly for five hours after administration of the barium—may demonstrate the lesion. In 6 of the 22 cases of malignant disease reported to

There had been no previous operations, and no significant loss of weight.

Examination revealed a well-preserved woman, who appeared moderately ill and complained of lower abdominal pain. The temperature was 99.8°F., the pulse 92, and the respirations were normal. The abdomen was

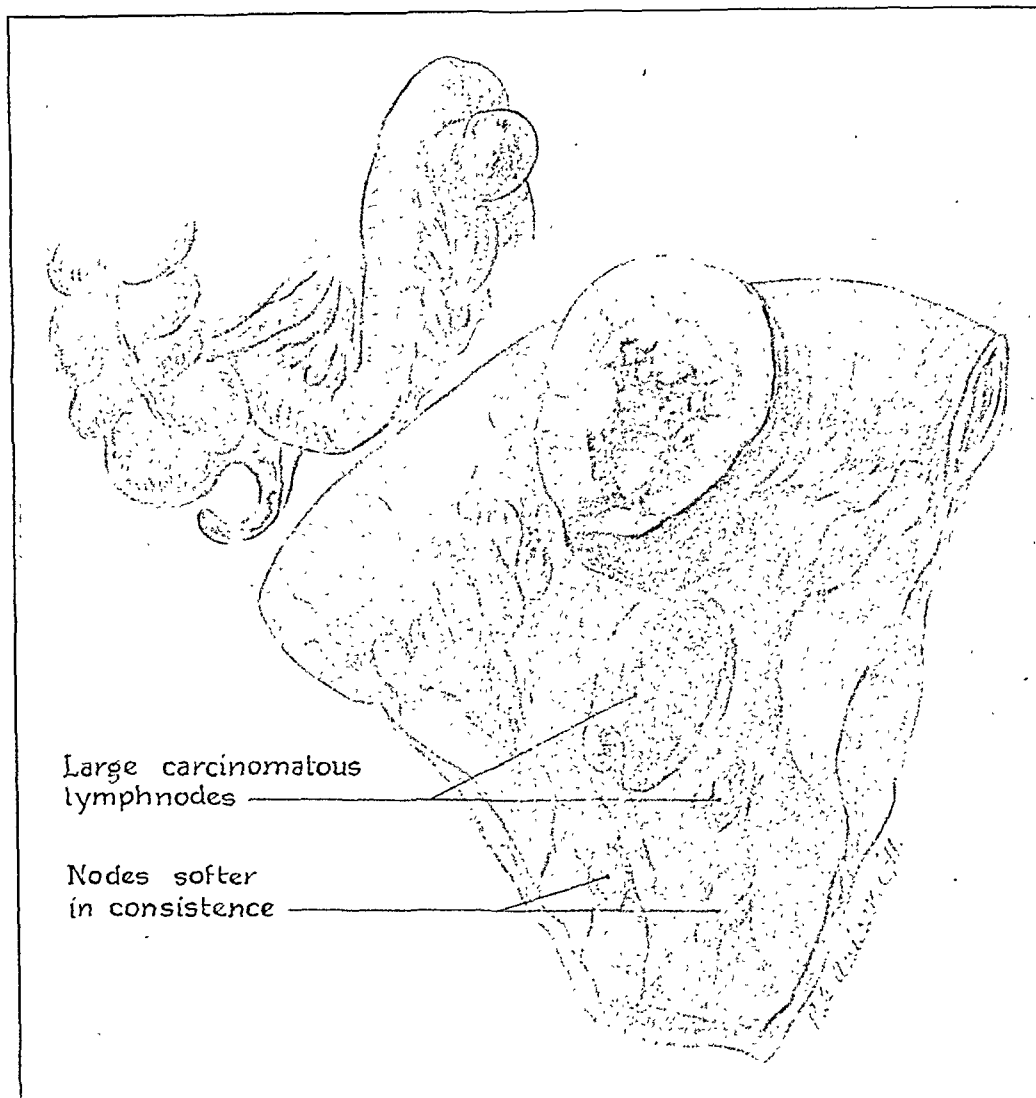


FIGURE 1.

date, the diverticular lesion was demonstrated roentgenologically.

#### CASE REPORT

Mrs. M.K., a 48-year-old Greek-American housewife, was admitted to the New England Baptist Hospital, under the care of Dr. Peter Comanduras, on November 24, 1940, with a chief complaint of abdominal pain of 3 days' duration. Except for intermittent abdominal discomfort for 17 years, for which she had had much medical care, the patient had been well.

For 3 days, there had been general abdominal pain of slight severity. This became worse 24 hours before admission and shifted to the lower abdomen, with tenderness and discomfort in both lower quadrants. There had been gradual development of slight distention and borborygmi, but no nausea, vomiting, constipation, diarrhea, fever or chills. The menstrual history was irrelevant.

moderately rounded and tympanitic, with definite but not marked distention. There were diffuse soreness and tenderness in both lower quadrants, without localized signs. Spasm was voluntary, and no mass was palpable. Manipulation of the uterus bimanually caused lower abdominal pain. However, there was no adnexal mass or tenderness, and there was no mass in the rectouterine pouch of Douglas.

The white-cell count was 9000, and urinalysis was normal. A diagnostic x-ray plate of the abdomen showed a moderate amount of air in the stomach and a lesser amount in the large bowel. There was no small-bowel distention. Gastrointestinal x-ray studies during the previous year had been reported as normal, and had not shown the presence of either a tumor or a Meckel's diverticulum. The clinical picture was regarded as atypical, and the tentative diagnosis of an acute surgical condition of the abdomen, probably acute appendicitis, was made.

Operation on the evening of admission by one of us (H. L. A.) was carried out through a right-lower-quadrant paramedian incision, with retraction of the rectus muscle laterally. A moderate amount of brown, turbid fluid without odor was encountered, culture of which produced no growth. Exploration revealed the viscera, including the large and the small bowel, to be normal except for the terminal ileum, 20 cm. from the cecum. On delivery of this portion of the bowel from the pelvis, there was a gush of yellowish exudate, resembling pus, but still without odor. At this part of the ileum, and arising 1 cm. from the mesenteric border, there was a firm, tensely filled, whitish, cylindrically-shaped 4-by-3-by-3-cm. mass, with markedly enlarged lymph nodes in the regional

somewhat soft and dark red. On opening of the bowel, the mucosa is entirely normal except for an opening 0.2 cm. in diameter. This communicates with a central lumen in the mass which projects into the mesentery. On section, this mass has a well-developed muscularis and a serosa, and is lined by mucosa continuous with mucosa of the bowel. From its base, an irregularly polypoid growth, covered with greenish exudate, protrudes into and practically fills the lumen. On section, this polypoid growth is 1 cm. thick, and shows gray, fibrous tissue, with scattered foci of necrosis extending out to the serosa, which at this point is yellowish gray. The remaining mucosa of the diverticulum is of normal thickness and communicates smoothly with



FIGURE 2.

mesentery. The adjacent nodes were hard and grossly carcinomatous, whereas the more distant nodes at the root of the mesentery were soft and edematous in appearance.

Resection of 30 cm. (12 inches) of the ileum was carried out, including a margin of 10 cm. of ileum on each side of the lesion. A V-shaped portion of the corresponding mesentery and enlarged lymph nodes was included in the resection. End-to-end anastomosis of the ileum was done, with the use of the Furness clamp. Precautionary ileostomy was performed by inserting a No. 20 catheter in the ileum 15 cm. proximal to the anastomosis. The catheter was then brought out through the omentum and a separate small stab incision in the abdominal wall. The incision was closed without drainage.

The pathological report by Dr. Shields Warren was as follows:

The specimen consists of a portion of ileum with adjacent mesentery, 30 cm. in length, which is essentially normal except for a firm and reddish mass, 3.5 cm. in diameter, extending into the mesentery (Fig. 1). The surface is smooth and rounded. Nearby, in the mesentery, is a firm, dull-gray mass measuring 3 by 2 by 2 cm., and a third mass 2 by 1 by 1 cm., which is

the mucosa of the ileum. The larger mass in the mesentery, on cut section, is homogeneous and yellow gray. The smaller mass, on section, is reddish gray and hemorrhagic.

On microscopic examination, the diverticulum is seen to have a well-developed muscularis; in the region of the tumor, this is heavily and irregularly infiltrated by masses of epithelial cells, which, in most places, form irregular glands (Fig. 2). Much of the inner aspect is completely necrotic and infiltrated by polymorphonuclear leukocytes and fibrin. Some of the tumor has penetrated the muscularis and is growing out into the mesentery. The cells of the tumor are irregularly but frequently cuboidal, or low columnar, and contain scattered mucous ductlets. The nuclei are oval and moderately vesicular, with usually a single prominent nucleolus. Mitoses are fairly frequent. In the diverticulum, there is no evidence of gastric mucosa.

Sections of the mesenteric masses show similar tumor tissue, with varying degrees of necrosis.

Diagnosis: adenocarcinoma arising from Meckel's diverticulum, with metastasis to two lymph nodes.

Convalescence was normal until the 11th day, when removal of the ileostomy tube was followed by brisk hemorrhage through the stab incision, which had been made

too close to the left inferior epigastric artery. The hemorrhage was controlled by a tight pressure dressing, however, without further intervention. The patient was discharged on the 21st postoperative day.

She has been seen periodically since then, the last visit being in June, 1941, 7 months after operation. A check-up gastrointestinal x-ray series, 3 months after operation, revealed a well-functioning anastomosis. At the last visit, the patient's general health was good, and there was no evidence of recurrence or metastasis.

This is the seventh case of carcinoma arising in a Meckel's diverticulum that we have been able to find reported in the literature. Most of these reports have been made in recent years. The previous 6 cases were reviewed by Nygaard and Walters<sup>1</sup> in 1937 (Table 1). Only 1 case, that re-

TABLE 1. Cases of Carcinoma Arising in Meckel's Diverticulum Reported in Literature from 1931-37.

AUTHOR	AGE OF PATIENT yr.	TYPE OF NEOPLASM	TREATMENT
Wiseley <sup>8</sup> (1931)	41	Medullary carcinoma	Removal
Copeland <sup>9</sup>	?	Adenocarcinoma (? of umbilicus)	Removal
Michael and Bell <sup>10</sup> (1932)	76	Adenocarcinoma	Removal
Franke <sup>11</sup> (1933)	54	Adenocarcinoma	Removal
Brown <sup>12</sup> (1933)	62	Medullary carcinoma	Removal
Gray and Kernohan <sup>7</sup> (1937)	37	Adenocarcinoma (arising from gastric mucosa)	Removal

ported by Gray and Kernohan,<sup>7</sup> showed the adenocarcinoma arising from gastric mucosa within the diverticulum.

In all 7 cases, removal of the diverticulum, tumor and regional metastatic areas was carried out, with reasonable expectancy of immediate salvage of these patients. Although more information regarding the late results in these patients would be helpful, it seems from this experience that the malignant tumor manifests no more rapid rate of growth than carcinoma of other portions of the intestinal tract. It also seems evident that the local complications usually produce symptoms early enough to allow timely radical resection of the growth before widespread dissemination occurs.

The need for generous resection of both intestine and mesentery well lateral to the growth is emphasized, to include any lateral lymphatic extension of the metastases around tumor-blocked lymph channels in the mesentery.

Reports of sarcoma arising within a Meckel's diverticulum have been more frequent, with 16 cases reported in the literature (Skinner and Walters<sup>2</sup>). Clinically, these sarcomas differ little from the carcinomas in that both give rise to symptoms when such complications ensue as ulceration, hemorrhage, obstruction by pressure or intussusception, and perforation. The sarcomas have usually been much larger primary tumors than the carcinomas, but most have been likewise resectable.

SUMMARY

Increasing clinical recognition of the many possible complications that may arise in a Meckel's diverticulum continues to stress the value of early control of these complications and even removal of the uncomplicated diverticulum whenever feasible. In the majority of cases, the complications are acute, and the diagnosis is uncertain or unsuspected. The responsibility therefore often lies heavily on the surgeon to recognize the lesion at operation, as in our patient. This may be difficult in the presence of marked obstruction, peritonitis or a large tumor, with or without metastases. Attention has been directed here to the occurrence of malignant neoplasms arising in a Meckel's diverticulum, more particularly to carcinoma, with the report of a case in which the growth was removed and an immediate successful outcome secured.

412 Beacon Street

REFERENCES

1 Nygaard, K. K., and Walters, W. Malignant tumors of Meckel's diverticulum: report of a case of leiomyosarcoma. *Arch. Surg.* 35:1159 1172, 1937.

2 Skinner, I. C., and Walters, W. Leiomyosarcoma of Meckel's diverticulum, with roentgenologic demonstration of the diverticulum. *Proc. Staff Meet., Mayo Clin.* 14:102-107, 1939.

3 Reiser, E. Duodenalinvagination hervorgerufen durch ein Meckelsches Divertikel. *Röntgenpraxis* 7:90-94, 1935.

4 Harkins, H. N. Intussusception due to invaginated Meckel's diverticulum: a report of two cases with study of one hundred and sixty cases collected from the literature. *Ann. Surg.* 98:1070-1095, 1933.

5 Greenblatt, R. B., Pund, E. H., and Charney, R. H. Meckel's diverticulum: an analysis of eighteen cases with report of one tumor. *Am. J. Surg.* 31:285-293, 1936.

6 Matt, J. G., and Timponi, P. J. Peptic ulcer of Meckel's diverticulum. *Am. J. Surg.* 47:612-623, 1940.

7 Gray, H. K., and Kernohan, J. W. Cited by Nygaard and Walters.<sup>1</sup>

8 Wiseley, A. N. Medullary carcinoma of Meckel's diverticulum. *J. A. M. A.* 96:1949, 1931.

9 Copeland, M. M. Cited by Wiseley.<sup>8</sup>

10 Michael, P., and Bell, H. G. Primary adenocarcinoma arising in a Meckel's diverticulum. *Surg., Gynec. & Obst.* 54:95-97, 1932.

11 Franke, K. Über ein primäres Carcinom in einem Meckelschen Divertikel. *Ztschr. f. Krebsforsch.* 39:206-216, 1933.

12 Brown, R. Carcinoma of Meckel's diverticulum. *S. Clin. North America* 13:1283, 1933.

## MEDICAL PROGRESS

### GYNECOLOGY: ENDOMETRIOSIS

JOE V. MEIGS, M.D.\*

BOSTON

IN this review, endometriosis and adenomyosis are considered two separate entities. Endometriosis is used to describe widespread areas of ectopic endometrium; an endometrioma is a single area of ectopic endometrium. Adenomyoma indicates the growth of tissue from the true endometrium into the myometrium, whereas adenomyosis indicates a diffuse involvement of the uterus. This is not an absolutely accurate division but, for the purposes of this review, will suffice. Adenomyosis is a fairly clear-cut entity with a satisfactory explanation, whereas great controversy still rages concerning endometriosis. Cullen<sup>1</sup> has shown that most uterine adenomyomas are due to the direct downward growth of endometrium into the myometrium, and direct connections were demonstrated in most of his cases. Adenomyoses or adenomyomas are often responsible for dysmenorrhea and abnormal bleeding, and are more frequently found in patients who have had many pregnancies rather than a few, in contrast to endometriosis. Adenomyosis is usually found in older women and is often reported from the laboratory when not suspected clinically. The treatment is, as a rule, removal of the uterus. Sometimes, adenomyomas are found as diffuse, fibroidlike areas in the uterus, but without capsules; they appear to be fibroids, but do not shell out of the myometrium as fibroids do. An adenomyoma is microscopically similar to an endometrioma.

Endometriosis is a very live topic principally because of Sampson's<sup>2-4</sup> epoch-making studies and, more recently, because of its apparent increase in frequency<sup>5</sup>—whether this is an actual increase or not, it is as yet impossible to state. Experimental work on the problem has been carried out and will be described later, but its true explanation is not yet established. Associated as it is with infrequent child bearing and sterility, it is of great importance to all. Endometriosis or endometriomas may be found in many areas, but nearly all are pelvic or close to the pelvis. The disease is rarely found outside the organs and peritoneum of the true pelvis, and yet there is no acceptable

reason why it should not be. Endometriosis has been found in the arm, the lung, the leg, the round ligament in the inguinal canal, the vulva, the cervix and the perineum, and the explanation of these lesions has not been satisfactory. All the pelvic organs and parts of the pelvic peritoneum have been involved, some for one reason and some for others.

#### SYMPTOMS AND DIAGNOSIS

The symptoms of endometriosis are well known. They may or may not consist of a definite group, or any one of the usual symptoms may be present, or there may be none at all. Typically, the patient complains of painful menstruation or at least of menstrual pain, abnormal flowing, a change in the type of period or backache. Examination may be negative, or there may be masses in the broad ligaments or nodules in the uterosacral ligaments when the patient is examined by rectum. A hard beady or shotty feeling in the cul-de-sac on vaginal or, especially, rectal examination may suggest the correct diagnosis. There has been very little new progress in the evaluation of symptoms or physical examination. Special nodules, such as those occurring in the vulva, groin, umbilicus and abdominal scars, frequently swell before the menstrual period, and this swelling with a definite rhythm usually makes the diagnosis easy. Lesions in the rectovaginal septum may be seen as red, buttonlike areas or as a conglomeration of blue spots; the diagnosis is easy if considered. Endometriosis of the bowel is never difficult to diagnose, for bleeding may occur and is usually rhythmic. The tumor is often behind the mucous membrane, and the x-ray picture may show uninjured bowel mucosa. The presence of acquired dysmenorrhea or premenstrual pain and the occurrence of a mass are very significant, and at operation the finding of characteristic puckered areas with blue spots or the presence of pelvic endometriosis should clinch the diagnosis of endometriosis in the bowel.

#### TREATMENT

There has been no outstanding contribution to the treatment of endometriosis. For years, it has been known that removal of the ovaries or their destruction by means of radiation stops the growth

Reprints of articles in this series are not available for distribution, but the articles will be published in book form. The current volume is *Medical Progress: Annual, 1940* (Springfield, Illinois: Charles C. Thomas Company, 1941, \$4.00).

\*Instructor in surgery, Harvard Medical School, chief of Gynecologic Service, Massachusetts General Hospital; gynecologist, Pondville Hospital.

of the tumors and allows atrophy to take place, as it does in the endometrium itself. The radical treatment is total hysterectomy, with bilateral salpingo-oophorectomy, and the conservative treatment is to excise the areas in the ovaries, peritoneum or other accessible places. If, after conservative treatment, recurrence takes place, radium or x-ray therapy will destroy the ovarian hormone output, and the lesions will atrophy. Excision of the small peritoneal lesions has long been carried out, and some observers have recently recommended the fine nasal cautery to destroy each of the small implantations found on the peritoneum. Since Cotte<sup>6</sup> advocated resection of the superior hypogastric plexus (presacral nerve) for dysmenorrhea, it has been obvious that this operation should be tried to check the pain of endometriosis; it has been advocated by many.<sup>7, 8</sup> Counseller<sup>9</sup> has lately changed his ideas and suggests its use only in cases of uterine adenomyosis, because from the knowledge of the areas affected by this nerve plexus it is unlikely that resection would stop the pain of endometriosis involving the broad ligament or other pelvic structures. Section of the nerve involves the uterus only, and therefore should relieve only uterine pain. Cooke<sup>10, 11</sup> has recognized this and carries out ovarian neurectomy to relieve ovarian pain by cutting the infundibular pelvic ligaments—the best way to section the sympathetic nerves of the ovary. If there is no damage to the ovary by interfering with the blood supply, it is much more reasonable to expect relief by this method than by resection of the presacral nerve.

The use of hormones to suppress menstruation completely by interfering with the pituitary gland should help, but such treatment cannot be carried on long enough to obtain any permanent result. Testosterone will suppress menstruation for months, but may cause growth of hair if too much is used, or if it is employed for too long a period. It is therefore not advocated. Estrin, which has been given to prevent ovulation<sup>12</sup> and thus prevent true or uterine dysmenorrhea, should prevent the pain of adenomyosis, but it should not affect the lateral masses of endometriosis that are responsible for flank pain. Sturgis<sup>13</sup> believes that the pain of endometriosis may be due to the premenstrual congestion that nearly always precedes menstruation and thus causes swelling of scarred and fibrotic endometrial lesions. Prevention of ovulation with estrin would not prevent edema, but testosterone, by inhibiting the pituitary gland and therefore all action on the ovary, will prevent edema and therefore eliminate painful swelling.

Treatment of endometriosis should therefore con-

sist in conservative surgery, with the destruction or removal of small areas of ectopic endometrium in women desiring children, or radical surgery in the older age group—that is, by removal of all involved tissue, with the preservation of ovarian function, radiation being used if growth continues. It is well to caution the operator who attempts to do a total hysterectomy to remember that in these cases the posterior cul-de-sac and the rectum may be pulled up and frozen to the back of the uterus at the level of the internal os; an attempt to free this cul-de-sac to allow an approach to the cervix may result in a hole in the bowel. It is far wiser, if one is confronted with an extensive case of endometriosis with its tough adhesions, to remove all tumor and organs that can easily be removed, and trust to radiation later, than to perforate the bowel in an attempt to do a radical removal.

#### RESULTS OF TREATMENT

The results of radical treatment are excellent. The subsequent menopause can be treated satisfactorily by ovarian hormones, although this treatment may stimulate the growth of remaining endometrial tissue. Conservative treatment results in from 9 to 26 per cent of reoperations.<sup>7, 14, 15</sup> Inasmuch as most conservative operations are done for preservation of childbearing, it is essential to note that from 9 to 32 per cent of patients<sup>14, 16, 17</sup> become pregnant subsequent to operation. There is no doubt of the value of conservative procedures, but it should always be explained to the patient that there is a definite possibility of radiation or further surgery. The relief of pain following conservative surgery is great, but in some cases, early reoperation has been necessary, and in others, late. The endometriosis progresses slowly but steadily under the influence of the ovarian hormone, estrin.

#### ETIOLOGY

The greatest interest in this entity concerns the theories of its etiology, about which many controversies still rage. The main one concerns whether Sampson's theory of tubal reflux is correct or not.

Of first importance is the fact that endometriosis or adenomyosis is a comparatively newly recognized entity. In 1897, Cullen,<sup>18</sup> at a meeting of the Johns Hopkins Hospital Medical Society, reported his first case of adenomyoma of the uterus. In 1897, Pfannenstiel<sup>19</sup> reported the first case of adenomyoma of the rectovaginal septum. Russell<sup>20</sup> reported, in 1899, the finding of endometrial tissue in the ovary; he also removed a

small, pea-sized nodule of endometrial tissue from the right uterosacral ligament. In 1918, Cullen<sup>1</sup> operated on a patient with an adenomyoma of the rectovaginal septum and a widespread growth of the sigmoid. In 1909, Meyer<sup>21</sup> reported the history of a patient, operated on by Mackenrodt for adenomyoma of the bowel, who had had a resection done. In 1921, Sampson<sup>2</sup> reported his first group of patients with perforating hemorrhagic cysts of the ovary and demonstrated the presence of endometrial tissue in them and in the pelvic peritoneum. In 1922, Janney<sup>22</sup> reported a group of patients with endometrium in the ovary. From the time of Sampson's first report, the literature has teemed with articles on endometriosis, a partial list of which is appended at the end of this review. Sampson has written by far the most numerous and most carefully prepared papers and has given not one but numerous theories of its development. However, the one that is usually regarded as his greatest contribution concerns the question whether or not endometrium can flow through the tubes during menstruation and become implanted on the ovary and peritoneum of the pelvis. Since Sampson's great paper, many other ideas of the etiology have been presented.

The theory of von Recklinghausen that adenomyosis and endometriosis are due to growth of left-over pieces of the Wolffian ducts has long been discarded. It is far likelier that these conditions arise from cell remnants following the formation of the Mullerian ducts. This will be discussed later. Ivanoff<sup>23, 24</sup> and Meyer<sup>25</sup> independently advocated the idea that the epithelium of the pelvis, inasmuch as it is the celomic epithelium from which the Mullerian ducts arise, can under certain circumstances, such as irritation due to inflammation or injury by menstrual blood, undergo metaplasia and produce Mullerian epithelium or endometrium. This theory is plausible and has many advocates. It explains most endometriosis satisfactorily. Heim<sup>26</sup> supports this theory by stating that endometriosis occurs only in tissue that is derived from the original celom. He believes that it may be derived from the mesothelium, endothelium or germinal epithelium of the early embryonic celomic cavity. Bell<sup>27</sup> and Robinson<sup>28</sup> actively join the theory of Ivanoff and Meyer, both believing that the celomic epithelium under certain circumstances may be the source of the ectopic endometrium.

Halban,<sup>29, 30</sup> in 1924, advanced the idea that pieces of tissue metastasized by way of the lymphatics, and suggested that the sites of endometriosis were best explained by lymphatic routes. It is true that this theory best explains the presence of endometrial glands in lymph nodes of the pelvis. In

operations for cancer of the cervix, such lymph nodes have been found and described. Taussig<sup>31</sup> has recently found such nodes in cases in which he has done pelvic lymph-node dissections following radiation treatment of cancer of the cervix. This method of extension of endometriosis may best explain the report of Büngeler and Fleury-Silveira<sup>32</sup> of endometriosis in the pleural cavity; however, extension to the chest cavity may also be explained by metastasis through the blood stream.

Sampson's various theories, some not generally known, are as follows:

During menstruation, pieces of tissue are cast off, and some of this tissue may flow in retrograde method through the tube and, being spilled out, may grow on the ovary or the peritoneum, where such particles may alight.

Pieces of endometrium may grow into the wall of the fallopian tube, or may be caught in the fimbrias of the tube and grow there.

The tubal mucosa itself may act in response to the ovarian hormones and may occasionally menstruate, and pieces of tubal epithelium may be implanted by contiguity on the ovary or any other structure it may touch.

An ovarian endometrial blood cyst may rupture and spill pieces of endometrium into the pelvis that may grow—Sampson agrees that there is no positive proof of this.

An endometrioma of the ovary may become attached to a pelvic structure, and because of the adherence to the peritoneum, areas of endometrium may grow into the contiguous peritoneum.

Cast-off endometrium may go so far as to implant itself in a hernial sac and thus may account for endometriosis in the groin found in a hernial sac.

It can also spread by way of the lymphatics and blood vessels, and thus find its way into the round ligaments.

There are many reasons for Sampson to believe in his major theory, for he has seen what he considers viable endometrial tissue surrounded by blood in the material flowing through the tubes at laparotomy. The lesions of the ovary are on the lateral and under surfaces, an especially good place for blood to strike the ovary as it comes out of the tube. He believes that peritoneal implants are so small that they do not participate so perfectly in menstruation as ovarian endometrial cysts. He also believes that, if the bits of endometrium carried into the pelvis through the tubes are dead, his theory is dead. His theory has support from the work of Bartelmez,<sup>33</sup> who on examining uteri removed and fixed immediately after laparotomy says that even the tissue fragments and cell masses free in the lumen on the first day of the menstrual flow have many cells that appear normal histologically. Such support is very satisfactory. However, the work of Markee<sup>34</sup> is extremely damaging to Sampson's theory. Markee transplanted living endometrium of the uterus of the monkey into the eyes of the same monkey and obtained a

very large percentage of takes. By this method, he was able to view menstrual cycle after cycle either by the naked eye or by microscope. He makes the following observation: "Although thousands of fragments were observed in the 432 menstrual periods studied since 1928, not a single re-implantation of a fragment was noticed. It was seen that the fragments settled to the bottom of the anterior chamber [of the eye] and disintegrated. Occasionally one would remain whole for 36 hours but most of them disappeared within one hour and many within 30 minutes." This suggests that, in the monkey, endometriosis cannot be due to the implantation of such fragments, which are not viable, at least not in the anterior chamber of the eye, although Cron and Gey<sup>35</sup> reported a growth of desquamated fragments in tissue culture. The work of Cron and Gey, to which a great deal of weight has been given in the past in support of Sampson's theory, is of questionable value, for the tissue that was grown on a plasmatic medium consisted of pieces of tissue obtained from a woman on the second day of the menstrual cycle that were removed by a *dull curette*. Leukocytes and connective cells and sheet-like outgrowths of epithelial cells were grown. The tissue was transplanted every four or five days for a month, but no increase in the mass of tissue occurred. In a footnote on the same paper, the authors state: "... additional experiments show that the fragments of epithelium [decidua menstrualis] normally found in the menstrual flow and obtained without the use of a dull curette, are visible. In general, as far as we have been able to determine, the decidua menstrualis, is more active when cultured in vitro than normal endometrium." No further reports have been found in the literature concerning the results of these later tissue cultures to enlarge on the footnote, and it is obvious, in view of Markee's work in the monkey, that this should be done, for proof is not present in the reported experiment.

In answer to the problem raised by Markee's work, many would say that the tissue of the eye is not similar to that of the pelvis, and yet it was possible to transplant endometrium into the eye easily. The work of Jacobson<sup>36</sup> demonstrates that the endometrium of the rabbit and the monkey will grow in the pelvis of those animals, more especially if the peritoneum of the pelvis is irritated or if the tumor is transplanted into the pelvic peritoneum. But such tissue will *not* grow in the remainder of the peritoneal cavity. Moreover, Jacobson found in some of his experiments that endometrium would grow after the ovaries were removed. However, the endometrium used was a transplantation, such as a skin graft and not an

implantation as one understands Sampson's theory, and it is difficult to explain how implantation could occur in the human being unless some irritation of the peritoneum had occurred. The tissue used by Jacobson in his work was viable endometrium and not cast-off menstrual tissue. His difficulty with such material, and his ability to grow it only in the pelvis and Markee's difficulty with the eye make one think that perhaps the pelvic epithelium has some special value as a grower of endometrium or that it has in itself the inherent power to growth, and that the areas of endometriosis are responses to injury, as suggested by the Iwanoff and Meyer theory, rather than true implantations. It is obvious that more investigation must be done along the lines of Cron and Gey and of Jacobson before Sampson's theory of the growth of cast-off endometrium can be accepted. In about half the cases, the small peritoneal implantation functions as the endometrium does; in the other half, the endometrioma resembles the basal layer of the endometrium, which does not function. If Sampson's theory is correct, it seems that, since the endometrium cast off by the uterus must have been from the functional layer (compact layer), its implantation in the pelvic peritoneum should function and should not appear or act like the basal layer. Perhaps the cast-off functional tissue becomes the nonfunctional basal type. It seems, however, as if this suggested that the two tissues, cast off endometrium and implant, are not the same.\*

There are three other recent reports of interest in the consideration of ectopic endometrium. Büngeler and Fleury-Silveira<sup>32</sup> report the presence of endometriosis in the pleural cavity, Naratil and Kramer<sup>37</sup> of endometriosis in the extensor carpi radialis muscle of the forearm, and Markee<sup>38</sup> of endometriosis in the left thigh. The explanation of the chest-cavity extension, as noted above, is probably by extension through the lymphatics or veins of the vascular system, but that of the thigh and arm cannot be explained on any other basis than extension by vein. Hobbs and Bortnick<sup>39, 40</sup> have shown that viable endometrium can be transplanted to the lungs by way of the veins and that it will grow in the lungs. This is experimental proof that venous metastasis is a possibility. Until the excellent work of Batson,<sup>41</sup> it has always been impossible to explain the extension of tumors from the pelvis to bones and certain organs except through the lung, which presupposes the growth of a metastasis in the lung and subsequent extension to the left heart, or the

\*On the other hand, Sturges<sup>33</sup> believes that function depends on blood supply and hence a satisfactory supply of estrin, and that the functional endometrium that implants itself in the pelvis may be nonfunctional if the blood supply is not sufficient.

presence of an open foramen ovale in the heart. Too many unexplained metastases occurred, and the work of Batson, who has demonstrated a vertebral venous system, has unraveled the difficulties. This system of veins leads directly from the pelvic organs to the bones or, by connecting veins, to the veins of the extremities, without going through the caval system. In this way, the lungs can be detoured, and an endometrioma in the leg and arm and possibly one in the pleural cavity can be explained. These cases and Batson's work are in support of those who believe in the venous metastatic theory of endometrial extension. If the cases with endometrioma in the leg and arm are authentic, and it seems as if they are, the possibility of venous metastasis is a very significant theory of endometriosis.

It has always been difficult to explain why the small endometriomas seen in the pelvis are, when not accompanied by ovarian endometriosis, usually in the midline. Certainly, the uterosacral ligaments are difficult places for cast-off endometrium to light on and grow, as is also the area at the reflexion of the bladder flap on the uterus. Yet these areas are frequently affected. Such cases are better explained by the development of embryonal rests in the celomic epithelium or by venous or lymphatic metastasis. If endometriosis is due to the reflux of endometrium in menstrual fluid, the absence of tumors on the anterior abdominal wall and among the intestines and in the mesentery is

greater percentage of endometriosis in private practice among well-to-do patients than in the wards of the Massachusetts General Hospital. It was suggested that the reason for this was earlier marriage and earlier childbearing in the hospital group than in the private group. It was thought that birth control and spacing of children were having a serious effect on the fertility of well-to-do young women. Lack of early marriage and childbearing in young women is serious, for endometriosis is often accompanied by infertility. Monkeys in the jungle mate as soon as they become of age and have offspring until they either physiologically cannot have any more or die, but some women go at least twelve years without interruption of their menstrual periods. This is not normal. Twenty-eight per cent of 400 private patients had histologic endometriosis, in contrast to only 5 per cent of the ward patients at the Massachusetts General Hospital (Table 1). Only 66 per cent of married women with endometriosis in private practice were fertile, whereas 94 per cent of the hospital patients were fertile (Table 2). Seventy-three per cent of the private and 42 per cent of the hospital patients had two or less children; 53 per cent of private and 12 per cent of hospital patients were twenty-five years of age or over when married. Sixty-five per cent of the private patients, and only 40 per cent of the hospital patients, who had endometriosis had menstruated over ten years before the first pregnancy. All in all, there is a

TABLE 1. *Incidence of Endometriosis.*

TYPE OF CASE	CONSECUTIVE ABDOMINAL GYNECOLOGIC OPERATIONS	ENDOMETRIOSIS MICROSCOPICALLY		ENDOMETRIOSIS GROSSLY		ENDOMETRIOSIS MICROSCOPICALLY OR GROSSLY	
		NO. OF CASES	PER CENT	NO. OF CASES	PER CENT	NO. OF CASES	PER CENT
All cases							
Massachusetts General Hospital	400	21	5	11	3	32	8
Private	400	112	28	32	8	144	36
Excluding cases past the menopause							
Massachusetts General Hospital	344	15	4	10	3	25	7
Private	357	108	30	31	9	139	39

hard to explain. Although the pelvis is the likely place for endometrium to rest when a woman is upright, it is not the dependent area in a woman lying on her stomach. A woman is quiet when sleeping, she menstruates when asleep, and at that time a reflux would be likelier, and implantation should occur more easily. Because endometriosis is not found in ventral areas and is nearly always in the pelvis, it is probable that the pelvic epithelium or celom has some special predilection for this lesion.

It was recently shown<sup>5, 42</sup> that there is a much

great difference between these two groups, and the great amount of endometriosis in the private group can be explained on the basis of delay of childbearing. These facts are evidence that menstruation during many years without interruption is the cause of endometriosis, and that it is due to the stimulation to growth of the celomic epithelium and its embryonal rests.

Another striking fact is that underdevelopment of the genital organs is a frequent accompaniment of endometriosis. Patients with congenital erosion of the cervix, severe dysmenorrhea and



juvenile organs are very apt to develop endometriosis earlier than those without such stigmas. This suggests that if the uterus and the cervix are underdeveloped, so also may be the pelvic peritoneum; such patients are thus likelier to harbor embryonal rests and therefore more frequently have endometriosis. Late childbearing may allow more years of reflux bleeding, but the problem is more fundamental than that, and avoidance of normal function seems to be the cause. The pelvic or celomic epithelium, which is the only re-

TABLE 2. *Data on Patients with and without Endometriosis.*

STATUS	PATIENTS WITH ENDOMETRIOSIS		PATIENTS WITHOUT ENDOMETRIOSIS	
	PRIVATE	M. G. H.	PRIVATE	M. G. H.
	%	%	%	%
Married .....	74	86	74	82
Fertile .....	66	94	83	85
Two or less children .....	73	43	49	50
At marriage, 25 years old or over .....	53	13	39	18
At first pregnancy, 25 years old or over .....	63	18	—	—
From marriage to first pregnancy, 2 years or more .....	69	—	67	—
From menarche to first pregnancy, 10 years or more .....	66	56	40	28
From menarche to endometriosis, 17 years or more .....	83	65	—	—
At onset of symptoms, 27 years old or over .....	96	60	—	—
Stigma of underdevelopment .....	28	—	15	—

gion that grows endometriosis, is probably stimulated to growth by abnormal physiologic function. It is therefore time to advocate the obvious — namely, that all women should marry early and bear children early.

\* \* \*

Many questions concerning endometriosis are still to be answered. For example, why do areas of ectopic endometrium menstruate when Bartelmez and Markee and others have shown that menstruation is such a complicated process, necessitating coiled arteries of a special type and the varied layers of the endometrium? Why does pain occur when the uterus is not involved? Why is it that small endometriomas in the peritoneum do not become large chocolate cysts? Why is endometriosis localized in the pelvis in nearly all cases? Can cast-off endometrium grow?

In recent years, the work of Batson demonstrating a vertebral venous system has been outstanding because it explains, by a detour around the lungs, the method of extension of malignant lesions as well as of endometriosis. The work of Markee and Bartelmez aids in the conception of menstruation and leaves a great deal of explaining to account for the action of ectopic endo-

metrium. The work of Hobbs and Bortnick, by showing the viability of endometrium after venous extension to the lungs, is of great value. Cron and Gey's work should be repeated in a larger series of cases, for their experiments do not seem to be proved. The fact that ectopic endometrium has been found in the pleural cavity, the arm and the leg suggests that the theory of the venous pathway for extension of endometrium may be correct. Finally, the great frequency of endometriosis in private practice as distinguished from hospital-ward cases makes the questions of late marriage and late childbearing of great significance.

Progress has been made in the understanding of these lesions, but a great deal of work remains to be done.

264 Beacon Street

## REFERENCES

- Cullen, T. S. The distribution of adenomyomas containing uterine mucosa. *Arch. Surg.* 1:215-283, 1920.
- Sampson, J. A. Perforating hemorrhagic (chocolate) cysts of the ovary. *Arch. Surg.* 3:245-323, 1921.
- Idem.* The life history of ovarian hematomas (hemorrhagic cysts) of endometrial (Müllerian type). *Am. J. Obst. & Gynec.* 4:451-512, 1922.
- Idem.* Ovarian hematomas of endometrial type (perforating hemorrhagic cysts of the ovary) and implantation adenomas of endometrial type. *Boston M. & S. J.* 186:445, 1922.
- Meigs, J. V. Endometriosis: its significance. *Ann. Surg.* 114:866-874, 1941.
- Cotte, G. La sympathectomie hypogastrique: a-t-elle sa place dans la thérapeutique gynécologique? *Presse méd.* 33:98, 1925.
- Counseller, V. S. Endometriosis: a clinical and surgical review. *Am. J. Obst. & Gynec.* 36:877-888, 1938.
- Pemberton, F. A. Resection of the presacral nerve in gynaecology. *New Eng. J. Med.* 213:710-714, 1935.
- Counseller, V. S. The clinical significance of endometriosis. *Am. J. Obst. & Gynec.* 37:788-797, 1939.
- Cooke, W. R. Discussion of Counseller.<sup>7</sup>
- Idem.* Discussion of Counseller.<sup>9</sup>
- Sturgis, S. H., and Albright, F. The mechanism of estrin therapy in the relief of dysmenorrhea. *Endocrinology* 26:68-72, 1940.
- Sturgis, S. H. Personal communication.
- Payne, F. L. The clinical aspects of pelvic endometriosis. *Am. J. Obst. & Gynec.* 39:373-382, 1940.
- Pemberton, F. A. Endometrioma of the female genital organs. *New Eng. J. Med.* 217:1-5, 1937.
- Turunen, A. Endometriosis externa und Sterilität. *Acta obst. et gynec. Scandinau.* 18:237-242, 1938.
- Idem.* Über die Klinik der Endometriosis externa. *Acta obst. et gynec. Scandinau.* 19:477-541, 1939.
- Cullen, T. S. Adenomyoma uteri diffusum benignum. *Johns Hopkins Hosp. Rep.* 6:133-157, 1897.
- Pfannenstiel, J. Über die Adenomyome des Genitalstranges. *Verhandl. d. deutsch. Gesellsch. f. Gynäk.* 7:195-199, 1897.
- Russell, W. W. Aberrant portions of the Müllerian duct found in an ovary. *Johns Hopkins Hosp. Bull.* 10:8-10, 1899.
- Meyer, R. Über entzündliche heterotope Epithelwucherungen im weiblichen Genitalgebiete und über eine bis in die Wurzel des Mesocolon ausgedehnte benigne Wucherung des Darmepithels. *Virchow's Arch. J. Path. Anat.* 195:487-537, 1909.
- Janney, J. C. Report of three cases of a rare ovarian anomaly. *Am. J. Obst. & Gynec.* 3:173-187, 1922.
- Iwanoff, N. S. Adenofibromyoma cysticum sarcomatodes carcinomatousum. *Monatschr. f. Geburtsh. u. Gynäk.* 7:295-300, 1898.
- Idem.* K. Voprosu ob Adenomiomakh Matki. 79 pp. St. Petersburg Thesis, 1897.
- Meyer, R. Adenomyosis, Adenofibrosis and Adenomyoma. In Veit, J., and Stoeckel, W. *Handbuch der Gynäkologie.* Vol. 6. 476 pp. Third edition. Munich: J. F. Bergmann, 1930. P. 356.
- Heim, K. Über die Entwicklung der Endometriose an Ort und Stelle. *Arch. J. Gynäk.* 152:269-311, 1933.
- Bell, W. B. Endometrioma and endometriomyoma of the ovary. *J. Obst. & Gynaec. Brit. Emp.* 29:443-446, 1922.
- Robinson, M. R. A critique on the histogenesis of heterotopic endometrial proliferation. *Surg., Gynec. & Obst.* 41:36-48, 1925.
- Halban, J. Hysteroadenosis metastatica (Die lymphogene Genese der sog. Adenofibromatosis heterotopica): vorläufige Mitteilung. *Wien. klin. Wchnschr.* 37:1205, 1924.
- Idem.* Hysteroadenosis metastatica: die lymphogene Genese der sog. Adenofibromatosis heterotopica. *Arch. J. Gynäk.* 124:457-482, 1925.
- Taussig, F. J. Effect of irradiation on normal and metastatic lymph nodes. *Am. J. Roentgenol.* 43:539-543, 1940.
- Büngeler, W., and Fleury-Silveira, D. Considerações Sobre a Patogenia das Endometrioses. *Arq. de cir. clin. e exper.* 3:169, 1939.

- 33 Bartelme G W. Histological studies on the menstruating mucous membrane of the human uterus. *Contrib Embryol* 24 143 186 1933
- 34 Markee J E. Menstruation in intraocular endometrial transplants in the rhesus monkey. *Contrib Embryol* 28 223 308 1940
- 35 Cron R S and Gey G. The viability of the cast of menstrual endometrium. *Am J Obst & Gynec* 13 645 647 1927
- 36 Jacobson V C. The intraperitoneal transplantation of endometrial tissue. *Arch Path & Lab Med* 1 169 174, 1926
- 37 Navratil E and Kramer A. Endometriose in der Armmuskulatur. *Klin Wchnsch* 15 1765 1770 1936
- 38 Mankin Z W. Beiträge zur Histogenese der Endometriose mit Hinweis auf eine besonders selten vorkommende Lokalisation im mittleren Oberschenkeltrichter. *Arch f Gynaek* 159 671 683 1935
- 39 Holbs J E and Bortnick A R. Endometriosis of the lungs experimental production of endometrial transplants in the lungs of rabbits. *Surg Gynec & Obst* 69 577 583 1939
- 40 Idem. Endometriosis of the lungs. *Am J Obst & Gynec* 40 832 843 1940
- 41 Batten O A. The Function of the vertebral veins and their role in the spread of metastases. *Ann Surg* 112 138 1940
- 42 Meigs J V. Endometriosis—a possible infectious factor. *Surg Gynec & Obst* 67 253 255 1938
- 43 Jacobson V C. The autotransplantation of endometrial tissue in the rabbit. *Am J Obst & Gynec* 5 281 1922
- 44 Idem. Further studies in autotransplantation of endometrial tissue in the rabbit. *Am J Obst & Gynec* 6 757 1923
- 45 Jayle F. Le solénome du ventre de la femme (myo-solénome, fibro-solénome solénome kystique). *Presse med* 42 1871 1934
- 46 Joffeotte T N A and Potter A L. Endometriosis as a manifestation of ovarian dysfunction. *Am J Obst & Gynec* 31 681 1934
- 47 Joseph. Endometriosis der Harnblase. *Zentralbl f Chir* 57 113 1930
- 48 Keene F E. Perforating ovarian cyst (Sampon's) with invasion of the bladder wall. *Am J Obst & Gynec* 10 619 1925
- 49 Keene F E and Kilmrough R A. Endometriosis. *J A M A* 9 1164, 1930
- 50 King E S J. The association of endometriosis with neoplasms of the ovary. *Surg Gynec & Obst* 49 433 1929
- 51 King W W. The clinical symptoms of pelvic adenomyomata. *Brit M J* 2 572 1924
- 52 Lewinski H. Beitrag zur Frage der Adenomyosis. *Zentralbl f Gynaek* 55 2163, 1931
- 53 Martin J P. Mûcheon L. and Pigeaud H. Endométriose gravidique de l'opari abdominale. *Presse med* 41 565 1933
- 54 Masson J C. Surgical significance of endometriosis. *Ann Surg* 102 819, 1935
- 55 Mayo C W and Miller J M. Endometriosis of the sigmoid rectosigmoid, and rectum. *Surg Gynec & Obst* 70 136 1940
- 56 Mengert W F. Endometrioma occurring in a postcesarean laparotomy scar. *J A M A* 99 169 1932
- 57 Meyer, R. Adenomyom von dem Serosae epithel ausgehend. *Zisch f Geburtsh u Gynaek* 54 193 1905
- 58 von Mikulicz Radetzki F. Endometriosen austerhalb der Geschlechtsorgane. *München med Wchnsch* 86 962 1939
- 59 Moench G L. The etiology of adenomyosis and uterine fibromyoma an hypothesis. *Am J Obst & Gynec* 18 682 1929
- 60 Mussey R and Butsch W L. Symptoms of pelvic endometriosis. *Am J Surg* 30 141 1935
- 61 Navratil E. Beitrag zur Frage der Extremitäten Endometriosen. *Klin Wchnsch* 18 905 1939
- 62 Novak E. The significance of uterine mucosa in the fallopian tube with a discuss on the origin of aberrant endometrium. *Am J Obst & Gynec* 12 484 1926
- 63 Idem. Pelvic endometriosis. *Am J Obst & Gynec* 22 826 1931
- 64 Idem. Pelvic endometriosis and its treatment. *Am J Surg* 33 472 1936
- 65 O'Keefe G D and Crossen R J. The autotransplantation of endometrial tissue in dogs. *J Missouri M A* 24 257 1937
- 66 Philipp E and Huber H. Neue Erkenntnisse zur Entstehung der Endometriose. *Deutsche med Wchnsch* 66 1242 1940
- 67 Phillips R B. Endometriosis vesicae. *J Obst & Gynec Brit Emp* 41 165 1934
- 68 Read C D and Roques F. After results of the operative treatment of endometrioma. *Proc Roy Soc Med* 22 1441 1929
- 69 Reck A. Zur Genese der Endometriome gleichzeitig ein Beitrag zur Kenntnis und zur Heilung einer ganz seltenen. *Zentralbl f Gynaek* 57 765 1933
- 70 Sampson J A. Inguinal endometriosis (often reported as endometrial tissue in the groin adenomyoma) in the groin and adenomyoma of the round ligament. *Am J Obst & Gynec* 10 462 1925
- 71 Idem. Heterotopic or misplaced endometrial tissue. *Am J Obst & Gynec* 10 649 1925
- 72 Idem. Peritoneal endometriosis due to the menstrual dissemination of endometrial tissue into the peritoneal cavity. *Am J Obst & Gynec* 14 472 1927
- 73 Idem. Ovarian metastasis with cancer of the uterine body. *Am J Obst & Gynec* 15 101 1928
- 74 Idem. Infected endometrial cysts of the ovary. *Am J Obst & Gynec* 18 1 1929
- 75 Idem. Pelvic endometriosis and tubal fimbriae. *Am J Obst & Gynec* 24 49 1932
- 76 Idem. The development of the implantation theory for the origin of peritoneal endometriosis. *Am J Obst & Gynec* 40 349 1940
- 77 Schm D H. Künstliche Endometriosen. *Arch f Gynaek* 155 217, 1934
- 78 Schumann E A and Parke W E. Endometriosis in laparotomy scars. *Am J Obst & Gynec* 28 222 1934
- 79 Schwarz Otto H. Discuss on of Counsellor. *Arch f Gynaek* 149 579 1932
- 80 Setz L. Über Genese Klinik und Therapie der Endometriose. *Arch f Gynaek* 149 579 1932
- 81 Settergren T. On endometriosis in the urinary bladder. *Acta Chir Scan* 73 317 1934
- 82 Tonkes E. Eine neue Meinung über die Entstehung der endometrioiden Heterotopien. *Zentralbl f Gynaek* 56 1151 1937
- 83 Tuthill C R. Malignant endometriosis of the ovary resembling arrhenoblastoma. *Arch Surg* 37 554 1938
- 84 Villard E. Regard J. and Contamin R. Du rôle des états endométriaux dans la pathogénie de la grossesse tubaire. *Gynec et obst* 33 305 1936
- 85 Vogt E. Über das Adenomyom und die Adenomyosis. *München med Wchnsch* 78 7043 and 2080 1931
- 86 Weiss A C and Foley J. Endometriosis perineo anal. *Brit Soc Obst et Gynec* 25 99 1936
- 87 Witherspoon J T. Hormonal origin of endometrioma. *Arch Path* 20 22 1935

## ADDITIONAL REFERENCES

- Cattell R B. Adenomyosis of the colon and rectum with intestinal obstruction. *New Eng J Med* 217 9 1937
- Collins C U. Adenomyomas of the rectoanal septum. *Illinois M J* 51 128 1927
- Councilier A S. Endometriosis. *Surg Gynec & Obst* 70 848 1940
- Dalton. Ovarian autografting for endometriosis. *Surg Gynec & Obst* 70 220 1940
- Dougal D. Endometriosis as a pathological and clinical problem. *Tr Edinburgh Obst Soc* 97 61 1937 1938
- Idem. The problem of endometriosis. *Am J Obst & Gynec* 35 3-7 1938
- Douglass M. Tumors of endometrial origin. *New Eng J Med* 199 305 1928
- Idem. Endometriosis in uterine cornua. *Surg Gynec & Obst* 49 138 1929
- Dreyfuss M L. Pathological and clinical aspect of adenomyosis and endometriosis. *Am J Obst & Gynec* 39 95 1940
- Duncan C J. Endometrioma of Bartholin's glands. *New Eng J Med* 211 24 1934
- Everett H S. Probable tular origin of endometriosis. *Am J Obst & Gynec* 22 1 1931
- Frankl O. Adenomyosis and Endometriosis. *Zisch f Geburtsh u Gynaek* 115 1 1937
- Fraser A D. Ectopic endometrium in a maceus rheus. *J Obst & Gynec Brit Emp* 36 390 1929
- Furst A and Skorpil F. Surgically important localizations of heterotopic endometriosis (Chirurgisch wichtige Lokalisation der heterotopischen Endometriosen). *Arch f Klin Chir* 179 485 1934
- Gardner H H. Pelvic endometriosis. *Northwest Med* 38 367 1939
- Glen P M and Johnston I J. Endometriosis of the ileum with chronic partial intestinal obstruction. *J A M A* 115 520 1940
- Goodall I R. Endometrioma interstitiale. *J Obst & Gynec Brit Emp* 47 13 1940
- Goodwin W H. Endometriosis. *South M J* 25 325 1932
- Graves W P. Relationship of ectopic adenomyomata to ovarian function. *Am J Obst & Gynec* 10 665 1925
- Green Armitage V B and Datta S K. Endometriomata the five clinical types. *Brit M J* 1 607 1933
- Hubbe K. Über einen Fall von endometrioider Wucherung am Nabel mit Schwesdrüsenwucherung mit Betrachtungen über die Genese. *Zentralbl f Gynaek* 55 1204 1931
- Halban J. Zur Diagnose der Adenomyosis und der Adenomyome der Gebärmutter. *Zentralbl f Gynaek* 57 961, 1933
- Harbuz H F. Clinical pathogen and experimental investigations of endometriosis. *Arch Chir* 130 20 1934
- Hasthorst G. Zur Klinik der endometrioiden Heterotopien (Adenomyosis) beim geschlechtsreifen Weibe. *Deutsche med Wchnsch* 55 1304 1929
- Idem. Zur Genese der Blasenendometriose. *Zentralbl f Gynaek* 57 3071 1933
- Henney W S. Adenomyosis of endometrial origin in the laparotomy scars following incision of the pregnant uterus. *Am J Obst & Gynec* 10 625 1925
- Henry J S. An endometrial growth in the right isbium myos. *Surg Gynec & Obst* 44 637, 1927
- Hofmann T. Zur Klinik der Endometriose. *Zentralbl f Gynaek* 63 1 1939
- Hill L L. Aberrant endometrium. *Am J Surg* 18 301 1937
- Holbs J E and Lazer M B. Primary endometriosis of the cervix uteri. *Am J Obst & Gynec* 42 509 1941
- Hoffbauer J. Adenomyosis uteri. *J Med* 17 348 1936
- Holtz F. Endometriome avec fistule gravidique. *Gynec et obst* 38 278 1938
- Hooper G. The diagnosis and treatment of endometriosis. *Canad M A J* 12 243 1940
- Huber H. Myom Sterilitat und Fertilitat. *Zentralbl f Gynaek* 63 760 1939
- Hunter J W A. Some observations on experimental endometrial grafts. *Brit M J* 1 797 1927

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTE-MORTEM AND POST-MORTEM RECORDS AS USED  
IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

### CASE 28041

#### PRESENTATION OF CASE

*First admission.* A thirty-three-year-old Lithuanian-American housewife entered the hospital because of increasing dyspnea.

She had been quite well until a year and a half before admission, when dyspnea on exertion developed insidiously, accompanied by a vague feeling of substernal oppression. Six months before entry, slight cyanosis began to accompany the episodes of dyspnea. The patient began to sleep with an extra pillow, and experienced occasional nocturia. Six weeks before she entered the hospital, a physician gave her "heart pills," which she took for two weeks, without improvement in her condition. She then noted for the first time that her legs and abdomen were swollen, and that she had gained 30 pounds in weight. Additional pills "for the edema" were given by the physician, without noticeable effect.

Prior to the onset of her illness, the patient had often taken long walks without difficulty. She had had "pleurisy" thirteen years before. She denied syphilitic or rheumatic disease and had never been told of any cyanosis or functional disability in infancy. Two siblings had died in infancy of unknown causes, and her father had died at fifty-four of a "heart attack." She had been married for thirteen years but had never been pregnant.

Examination showed an obese, plethoric, quite cyanotic woman in moderate respiratory distress. The heart was enlarged, especially toward the left, with a diffuse apical impulse. The rhythm was regular. The heart sounds were distant, with accentuation of the pulmonic second sound. There was a systolic murmur, best heard at the left border of the sternum. The lungs were normal. The abdomen was distended, and slight shifting dullness was present in the flanks. The liver and spleen could not be felt. There was pitting edema of the lower extremities, and of the abdominal wall below the waistline. There was questionable distention of the veins of the neck. The fingers showed no clubbing.

The temperature was 98°F., the pulse 100, and

the respirations 35. The blood pressure was 140 systolic, 110 diastolic.

Examination of the blood showed a red-cell count of 5,200,000 with 19 gm. hemoglobin, and a white-cell count of 8880 with 73 per cent polymorphonuclears. Oxygen studies of arterial whole blood showed 93 per cent saturation; the carbon dioxide combining power of the plasma was 70.7 vol. per cent. The cell volume was 51.3 per cent. The urine showed ++ to +++ tests for albumin on eleven out of twelve examinations. Only occasional red or white cells appeared in the urinary sediment.

In a roentgenogram of the chest, the heart appeared enlarged, without any characteristic configuration. The left main bronchus seemed slightly elevated. There was fluid in both pleural cavities.

The electrocardiogram demonstrated right-axis deviation. In Lead 1, the QRS complex was slurred, and the T wave was flat. In Leads 2 and 3, the T wave was inverted, with sagging of the ST segment. The PR interval was 0.19 second.

The patient was treated with bed rest, and with restriction of fluid and salt intake. Rapid digitalization was accomplished, and Mercupurin was given intravenously every few days. An oxygen mask was used almost constantly at first, with marked improvement in the cyanosis. The diet was restricted to 800 calories daily, with added thiamin chloride, nicotinic acid and cevitamic acid. There was satisfactory diuresis, the weight dropping from 220 to 165 pounds in the course of a month's stay in the hospital.

*Final admission* (three months later). After the patient's discharge from the hospital, she was followed in the Out Patient Department. The dietary restrictions were maintained, and the patient continued on digitalis. She felt improved for the next two months, after which she was again troubled by cyanosis and dyspnea on exertion. The next week, she remained in bed, taking ammonium chloride. She slept poorly because of orthopnea. Because of increasing breathlessness, she re-entered the hospital.

Examination showed extension of the area of cardiac dullness, which was 15 cm. to the left of the midline at the apex, and 8 cm. at the level of the third interspace. A blowing murmur at the third left interspace filled all of systole. A rushing diastolic murmur was audible at the apex when the patient was placed in the upright position. The pulmonic second sound was split, and louder than the corresponding aortic sound. The border of the liver lay three fingerbreadths below the costal margin. The legs were cold, and

puting edema extended as far as the chest

The blood pressure, temperature, pulse and respirations were approximately as before.

During the night, although the patient was kept in an oxygen tent, she remained cyanotic. Early the next morning, she suddenly began to gasp and died within a few minutes.

### DIFFERENTIAL DIAGNOSIS

DR T. DUCKETT JONES: I wondered briefly if the increasing dyspnea in episodes could have been due to asthma. However, the patient had been examined within a reasonable period of the onset of her illness, and nothing had been found.

The dyspnea on exertion and the vague feeling of substernal oppression were, I presume, early symptoms of left-sided failure.

Cyanosis then assumed a greater part in the picture. The only feature that seems to be left out of the ordinary development of left-sided failure is cough, which the patient apparently did not have.

The swollen legs and abdomen and the increase in weight indicate further progression of heart failure.

"Prior to the onset of her illness, the patient had often taken long walks without difficulty." I suppose that this indicates that she was actually well up to thirty-one and a half years of age, or eighty-eight months before the onset of symptoms.

She had pleurisy thirteen years before admission. The history of pleurisy with pain does not help determine what the actual diagnosis was at the time.

Apparently, congenital heart disease was thought of because of the findings that later developed, and the note concerning well-being in infancy was put in to indicate that there was no evidence early in life of congenital heart disease.

"Examination showed an obese, plethoric, quite cyanotic woman in moderate respiratory distress." There seems to have been more cyanosis than is routinely seen in ordinary heart failure.

"The rhythm was regular." That is very important.

There was a loud pulmonic second sound, at the age of thirty-three. That probably represented some increased pulmonary pressure.

The systolic murmur at this stage means nothing to me; it is not at all unusual in various types of heart disease and in normal hearts. The murmurs described throughout are confusing. Gouley<sup>1</sup> has pointed out that basal systolic murmurs may have some role in pulmonary disease, which certainly comes in as one of the features of differential diagnosis later on in this case.

So far, everything fits congestive heart failure quite well. Why the liver was not felt, I do not know. The ascites apparently was not tremendous, so that one would believe that the liver was not palpable.

"The fingers showed no clubbing." Congenital heart disease in adult life is usually associated with clubbing of the fingers.

I suppose the elevated diastolic pressure might go along with peripheral failure, which the patient obviously had.

The carbon dioxide combining power of the plasma was about 10 vol per cent above normal, which is probably consistent with congestive failure. There was a distinct increase in the cell volume, indicative of hemoconcentration.

In the absence of further reports of urinary sediments and since no blood chemical findings were reported, I presume that the renal picture was the result of congestive heart failure, rather than primary renal disease.

Obviously, there was right-sided and left-sided enlargement of the heart by roentgenogram. The slightly elevated left main bronchus makes one think of a large left auricle, which is frequently associated with mitral stenosis. Both pleural cavities had some degree of fluid, although the amount is not stated.

The electrocardiogram demonstrated right axis deviation. I take it from the original description of this patient that she was not of the stature that would normally have right axis deviation of the heart. She was apparently an obese, short, stocky person, and might conceivably exhibit left axis rather than right axis deviation. Thus, the finding is significant and indicative of right-sided heart damage, of either a temporary or a permanent character.

The inverted T wave and the sagging ST segment suggest that the patient received digitalis shortly before entry into the hospital.

In view of the fact that the majority of patients with congestive failure do not require oxygen therapy, I should assume that the cyanosis was out of proportion to the ordinary features of failure observed in this case.

The restricted diet was probably prescribed on the basis of obesity—to decrease the patient's weight, as well as to get rid of edema fluid by other methods. There is no evidence that the heart status was due to the so-called "beriberi heart."

The patient must have been broad-chested to have a 15 cm left border. The left heart border was obviously well in the axilla, probably with some auricular and left ventricular enlargement.

The murmur of mitral stenosis is not often described as a rushing murmur. I do not know whether the rushing murmur was high or low pitched. I know that the murmur of mitral stenosis is heard better with the patient recumbent in the left lateral position than with the patient erect. I know that a blowing diastolic murmur, from aortic regurgitation, or possibly a basal diastolic blowing murmur, which may be called or considered a Graham-Steele murmur, is heard best in the erect position. Hence, the description of the murmur confuses me considerably. However, one can state that there was a change or progression in the decreased function of the heart in this case.

"The pulmonic second sound was split, and louder than the corresponding aortic sound," again indicative of an increase in pulmonary pressure.

"The border of the liver lay three fingerbreadths below the costal margin." This, together with the extensive peripheral edema, certainly indicates right-sided failure.

This picture is distinctly confusing. There is no history of preceding congenital defects, and many types of heart disease that one thinks of do not fit the picture very clearly. We can comparatively easily rule out the nephritic possibilities; the patient did not have hypertension at the end, and there is no evidence of uremia. The ordinary hypertensive syndrome, with a progressive course over a period of less than two years, would probably have exhibited hypertension at the end, and it is likely that the breaks in compensation would have been more acute and accompanied by more sudden episodes of left-sided failure and generalized symptomatology before the patient would have been bedridden. In addition, she had enlargement of both sides of the heart by x-ray and by physical examination, as well as right-axis deviation, which indicates that there was some right-sided dilatation.

Coronary disease, I think, we can reasonably dismiss. There was no acute episode. This does not always occur, but the patient did not have a low blood pressure at any time. There was never any severe pain, and the electrocardiographic picture is not characteristic of coronary disease.

Cor pulmonale, either acute or chronic, must be thought of. Acute cor pulmonale can be ruled out because there was no severe acute episode indicative of extensive infarction or thrombosis. The patient had no shock, no severe pain and no hemoptysis and she did not have the typical electrocardiogram of an acute cor pulmonale. So far as chronic cor pulmonale is concerned, the possibility of Ayerza's disease, which the cyanosis sug-

gests, can be ruled out on the fact that she did not have so long a period of decreasing pulmonary reserve as is observed in most cases of pulmonary fibrosis. The feature most in favor of cor pulmonale of more chronic form is the right-axis deviation.

Certainly, this is not the picture of syphilitic heart disease.

That leaves a large group of cases of heart disease — the rheumatic. In addition, there remain other types, such as unusual tumors, which I am not qualified to discuss. So far as rheumatic fever is concerned, the patient was fairly young and had had no previous rheumatic history. In rheumatic heart disease discovered for the first time in adult life, mitral stenosis is usually present; it is almost the characteristic feature of slowly or insidiously developing rheumatic heart disease, and is often accompanied by relatively little cardiac hypertrophy. The patients with mitral stenosis who have failure in middle life usually develop auricular fibrillation. In rheumatic heart disease with mitral stenosis for years, with hypertrophy probably as the result of myocardial change of previous attacks of rheumatic fever, there are often embolic phenomena, of which there is no evidence in this case. No murmur of mitral stenosis was heard when the heart rate was 100, and there was no failure. Save for one possibility, I believe we can discard the possibility that mitral stenosis was present. A large left auricle, as suggested by x-ray examination in view of the elevation of the left main bronchus, if practically occluded by thrombus, might occur along with mitral stenosis, even in the absence of the typical murmur. I think this is a possibility, although a remote one. So far as the symptoms of straight rheumatic heart disease and the usual picture of rheumatic fever are concerned, I think they do not exist. Young children or young adults with rheumatic infection who die as a result of acute carditis practically always exhibit right-sided heart failure first and progress to left-sided failure. Evidence of the former develops in the absence of pulmonary symptoms. Such patients do not have dyspnea, and lie flat in bed. The patient under discussion did not exhibit this picture. She had symptoms of left-sided or pulmonary difficulty, in addition to obvious cardiac hypertrophy. Parker and Weiss,<sup>2</sup> in 1936, reported a case of mitral stenosis with pulmonary hypertension, and pulmonary-artery sclerosis, with extensive changes throughout the larger and smaller vessels and arteriolar system of the lung. They considered the changes that they described to be comparable to changes seen in the systemic arterioles in malignant hypertension and

to be capable of developing very quickly in two months. Evidence was presented, aside from the one case given in detail, of the fact that in mitral stenosis there are often changes in lung tissue. Gouley,<sup>1</sup> who has written extensively of the alterations in the lung in rheumatic fever, points out that the pulmonary artery changes are not necessarily constant and dependent on the presence of mitral stenosis. They may be the result of a coincidental vessel and parenchymal change during active rheumatic fever. Gouley describes at great length the rubberoid lungs of chronic rheumatic fever, consisting of a parenchymal thickening and elastic-tissue weakening and hyperplasia. He also describes acute pulmonary consolidation,—so-called "rheumatic pneumonia or pneumonitis,"—which this patient did not have at any time. An acute pulmonary rheumatic process is not essential for such vascular changes to be found at autopsy. In autopsies of rheumatic-fever patients, we have seen practically all the lesions Gouley has described. We have never been entirely convinced that pulmonary changes in rheumatic fever are usually the primary reason for failure in adult life. Except for episodes of acute left-sided failure in adult mitral stenosis, I believe that the valve lesion itself in rheumatic heart disease usually has little to do with failure, but in this case we have a patient with no known rheumatic fever who was ill for less than two years, and who had both right-sided and left-sided failure. If this patient had been fifteen, sixteen or seventeen, it would not have disturbed me too much, despite the fact that there was no clinical evidence of active rheumatic fever—joint pains and so forth. To my mind, there is one syndrome, with changes probably in the heart itself and in the lung, that can produce this picture—namely, a very low-grade rheumatic process. Aschoff bodies may not be found, since the process in the myocardium is a very chronic one and the pulmonary picture is apparently more important than the myocardial. This patient may represent the unusual case in which chronic rheumatic-fever pulmonary changes are of primary significance. My clinical impression is that rheumatic fever could account for this picture, and as a second bet I should say that some unusual type of congenital anomaly might explain the picture.

DR GEORGE W. HOLMES: One or two things brought out in the films are not mentioned particularly in the notes, and I think they will help Dr Jones a little. The extreme narrowing of the supracardiac shadow is very much in favor of his interpretation. I cannot imagine a supra-

cardiac shadow so small as that in the presence of hypertension of any extent. In some of the films, there is evidence of either thickened pleura or fluid, as mentioned in the notes. Nothing was said about this change in the lung itself. I assume that this was attributed to fluid in the pleural space behind the area we are speaking of; however, it does not look like fluid, and one wonders if there was, at some time, some injury to that lobe, such as an infarct. The striking thing about the heart is the dilatation of the auricles.

DR. TRACY B. MALLORY: Does anyone want to hazard another diagnosis?

DR. WILMAN RICHARDSON: I want to hazard one. I think Dr. Jones mentioned it and excluded it, but I wonder whether pulmonary arterial obstruction, possibly on the basis of pulmonary thrombosis, in a patient of this age should not be seriously considered as more likely than rheumatic fever.

DR. JONES: You mean blocking the large vessels?

DR. RICHARDSON: An extending thrombosis.

DR. MALLORY: Dr. Bland, you saw this patient. Should you like to comment?

DR. EDWARD F. BLAND: About once a year, Dr. Mallory presents a very puzzling case of this nature. Several of us had followed this patient's course in the Cardiac Clinic, and she died on the medical ward when I was on service.

There are two important points in the history, whose sequence, I think, needs emphasis: the patient was breathless for a full year before she began to be cyanotic; thereafter, the cyanosis slowly progressed and at the end was extreme. Most of us considered seriously only two diagnostic possibilities: either some unusual congenital anomaly or primary disease of the pulmonary arteries. The clinical course was distinctly against the first and strongly suggested the latter. For the sake of the record, it should be stated that the arterial blood studies on this patient were done after she had been in an oxygen tent, and this alters the results considerably. Throughout her course, the physical signs suggested severe pulmonary hypertension, for which we could find no obvious explanation; we therefore concluded that this was obliterative pulmonary arterial disease and chronic cor pulmonale.

#### CLINICAL DIAGNOSIS

Cor pulmonale.  
Pulmonary endarteritis.

## DR. JONES'S DIAGNOSIS

Rheumatic fever, with extensive pulmonary changes, or  
Possibly, congenital heart disease.

## ANATOMICAL DIAGNOSES

Cor pulmonale.  
Hypertrophy and endarteritis of pulmonary arterioles.  
Infarcts of the lung, small.  
Pulmonary congestion, extreme.  
Chronic passive congestion.  
Peripheral edema.

## PATHOLOGICAL DISCUSSION

DR. MALLORY: It is very easy to cite the anatomic facts, but much more difficult to interpret them. This patient was found to have marked cor pulmonale; the right ventricle was from two to three times the normal size, and despite the marked dilatation, its wall measured 10 mm. in thickness against the normal of 4 mm. The pulmonary conus was distinctly dilated, although the main pulmonary artery was not. The branches within the lung, however, certainly were, and plaques of atheroma were very numerous. When we cut across the lungs, all the small vessels stood out prominently, had obviously thickened walls, and remained patent rather than collapsing as pulmonary arterioles ordinarily do. The lungs were heavy, and considerable amounts of fluid could be expressed from them. The mitral and aortic valves were absolutely normal. There was a slight question of minimal scarring of the tricuspid valve, but it was of normal diameter.

Microscopic examination of the heart showed nothing that would suggest acute rheumatic heart disease. On the other hand, microscopic examination showed the characteristic lungs of mitral stenosis. The alveolar walls were extremely thick and extremely edematous, and all the alveoli were filled with heart-failure cells. The pulmonary arteries were markedly hypertrophied; a few of them were thrombosed, but only a very few. I do not believe that one could claim on a quantitative basis that there were enough thrombosed pulmonary arteries to account for the right ventricular hypertrophy, and the type of change in the pulmonary arteries is much more what I should think was secondary to pulmonary hypertension than an obliterative endarteritis that might be the primary cause of a pulmonary hypertension. The mechanism by which all this is produced is completely beyond me.

DR. HOLMES: Was there anything in the right lower lobe?

DR. MALLORY: A small infarct.

## REFERENCES

1. Gouley, B. A., and Eiman, J. The pathology of rheumatic pneumonia. *Am. J. M. Sc.* 183:359-381, 1932.
2. Parker, F., and Weiss, S. The nature and significance of the structural changes in the lungs in mitral stenosis. *Am. J. Path.* 12:573-598, 1936.

## CASE 28042

## PRESENTATION OF CASE

A twenty-one-year-old Italian-American truck driver entered the hospital complaining of shortness of breath.

He had been well until six months before entry, when he began to tire easily. He felt weak, became dyspneic on slight exertion, and therefore quit work. Three months later, he was troubled with swelling of the face, ankles, penis and scrotum, which progressed until he experienced difficulty in urinating. Because of this, he consulted a physician, who gave him a course of thyroid, with resultant loss of about 10 pounds in weight. The swelling, however, persisted.

Two months before entry here, the patient was admitted to another hospital. His heart was found to be enlarged, extending 11 cm. to the left of the midsternal line in the fifth interspace. The rhythm was regular, with a rate of 51; the sounds were clear. The blood pressure was 112 systolic, 86 diastolic. Extension of the liver edge two or three fingerbreadths below the costal margin seemed likely, but could not be established with certainty, because of the obesity of the patient.

The blood showed a red-cell count of 5,400,000 with 109 per cent hemoglobin, and a white-cell count of 13,300 with 74 per cent mature polymorphonuclears. The blood Wassermann reaction was negative. The blood levels of cholesterol, sugar, nonprotein nitrogen and creatinine and the albumin-globulin ratio were within normal limits. The urine had a low specific gravity, and contained a slight trace of albumin, and occasional red and white cells and casts. Congo-red and phenol-sulfonphthalein excretion tests were negative. The basal metabolic rate was -19 per cent.

A roentgenogram of the chest showed enlargement of the heart involving predominantly the left auricle and ventricle, and an apparent interlobar effusion between the middle and upper lobes of the right lung. A roentgenogram of the skull showed a normal sella. An intravenous pyelogram was negative. An electrocardiogram showed complete heart block, with abnormal ventricular complexes, including marked inversion of the T waves in Lead 4, and a very long QT interval.

The patient was continued on thyroid and was also given ammonium chloride and vitamin B complex. He was kept on a low-calorie diet.

When discharged a month after admission, he had lost 28 pounds in weight and had become free of edema and dyspnea. Following discharge from the other hospital, he remained at home, out of bed, taking thyroid and vitamin B complex. He gradually became orthopneic at night, and began to cough frequently, bringing up fairly large amounts of frothy sputum. Six months after the onset of his illness, and five weeks after discharge from the other hospital, the patient entered this hospital.

An older sister had been studied previously at the same hospital because of the strikingly similar complaints of unexplained dyspnea and edema of the ankles, face and abdomen. Her heart was much enlarged, and in complete block, as shown by the electrocardiogram. The basal metabolic rate was -4 per cent. She was twice tapped for ascites. Death occurred about a year after onset of her illness. At the time the patient entered this hospital, a younger brother was just beginning to complain of dyspnea. He had been gaining weight. Some years previously, a physician found that he had a "large liver," during the course of an appendectomy.

On examination, the patient appeared normally developed and somewhat obese. He was orthopneic, but was not acutely ill. His complexion was ruddy. There was moderate edema of the eyelids, sacral soft tissue and both ankles. There was shifting dullness in both flanks. The liver did not pulsate, and its edge was smooth and was felt three fingerbreadths below the costal margin. The veins in the neck seemed slightly distended. Cardiac dullness extended into the axilla, with a diffuse apical impulse at the anterior axillary line in the fifth interspace. A soft systolic murmur was present at the mitral area. The rhythm was regular. The lungs seemed normal.

The temperature was 100.2°F., the pulse 50, and the respirations 24. The arterial blood pressure was 112 systolic, 80 diastolic. The venous pressure was equivalent to 250 mm. of water, in the right antecubital vein.

Examinations of the blood and urine were essentially the same as those at the other hospital. An electrocardiogram again showed complete block, with an auricular rate of 110 and a ventricular rate of 45. The T waves were flattened. A roentgenogram of the chest was similar to the earlier film, so far as the heart was concerned. There was also an area of increased density in the right cardiophrenic angle anteriorly, adjoining the diaphragm.

The patient became progressively more dyspneic. Three days after admission, Cheyne-Stokes breathing developed. The next day, there were several coughing spells in which the patient brought up

blood-streaked sputum. He complained of pain in the left calf, and the leg was tender to palpation. The temperature varied between 99 and 102°F. On the evening of the fourth hospital day, he had a number of transient convulsive attacks in which his eyes rolled upward and respirations became rapid and gasping. Two hours later, he expired.

#### DIFFERENTIAL DIAGNOSIS

DR. ASHTON GRAYBIEL: The medical history in this case begins with the appearance of symptoms without obvious cause; there is no story of any antecedent illness. Weakness and dyspnea, the first symptoms, were soon followed by massive edema. At that stage of the illness, kidney disease, as well as heart disease, was probably considered. Chronic nephrosis seems to be ruled out by the small amount of albumin found in the urine and the normal albumin-globulin ratio. Similarly, a nephrotic type of glomerulonephritis appears to be unlikely because of the relatively unimportant urinary findings and the normal blood pressure, nonprotein nitrogen and kidney function. Amyloid disease may involve the heart as well as the kidneys and other organs, and heart failure as a result of amyloid disease has been described. However, there is no known background for the development of amyloid disease, and the blood and urinary findings do not suggest amyloid nephrosis.

The electrocardiographic findings are of more than passing interest; it would be helpful to know whether there was any abnormal axis deviation.

DR. PAUL D. WHITE: The abnormality consisted of bundle-branch block, with left-axis deviation and low voltage of the QRS waves.

DR. GRAYBIEL: In the presence of bundle-branch block, axis deviation cannot safely be relied on for the determination of ventricular preponderance. The very long QT interval deserves comment. It may be quite long in heart block—as long as 0.5 second. It is abnormally long in hypocalcemia, in certain types of severe heart disease with marked dilatation of the heart, and in other pathologic states. Complete auriculoventricular block in any type of heart disease is relatively uncommon: a few years ago, we had observed only 72 cases in this hospital. It is of interest that 4 of these 72 were undoubtedly of congenital origin, and this was the likely etiology in 2 others (over 8 per cent). One of the 6 cases of complete heart block of congenital origin was in an infant whose twin brother had high-grade heart block with a slow ventricular rate. In the case under discussion, the possibility of congenital heart block must be strongly considered; it is very unusual to have complete auriculoventricular block in two young



siblings on the basis of any type of heart disease other than congenital.

May we see the x-ray films?

DR. JAMES R. LINGLEY: We do not have the previous x-ray films for comparison. These films show gross enlargement of the heart, the enlargement being general but most marked in the region of the left ventricle. There is also distinct prominence in the region of the left auricle. This shadow in the right cardiophrenic angle interests me very much because we have seen right-sided diaphragmatic hernias that looked like that. There may be herniation of the transverse colon through the right side of the diaphragm, or a herniation of the omentum. A barium enema was advised, but evidently the patient was too ill to have that examination. It could have been a pericardial cyst or a localized encapsulation of fluid, but both possibilities are unlikely.

DR. GRAYBIEL: Do you think that there was pericardial effusion?

DR. LINGLEY: I do not believe that there was any pericardial fluid.

DR. GRAYBIEL: The coughing spells shortly before death—which raised blood-streaked sputum and were associated with pain and tenderness in the calf—raise the question of pulmonary emboli. It is even conceivable that the illness began with an embolus that lodged in the pulmonary artery and caused preponderant right-sided heart strain and congestive failure; such cases have been described.

Finally, the terminal event may have been due to the breaking away of a mural thrombus from the left ventricle, with embolism to the brain, or death may have resulted simply from the severe degree of congestive failure.

We have, then, the unusual story of a young man who, within six months, developed heart failure and died. This story becomes the more remarkable when it is learned that a sister died of a similar illness and that both had complete auriculoventricular block. The degree and extent of the edema suggests either a severe grade of predominantly right-sided heart failure or some mechanical obstruction on this side.

It seems to me that a diffuse myocardial process must be considered as the possible cause of the signs and symptoms described. A number of cases of myocarditis of essentially unknown origin have been observed. "Isolated myocarditis" and "interstitial myocarditis" are terms sometimes used.

There is no good evidence that the heart disease was of rheumatic origin: there was no fever or joint pains, and murmurs were not heard until the terminal stages. Fiedler's myocarditis might

be mentioned, but fever is a characteristic of this disease. Syphilitic myocarditis is unlikely, not only because of its rarity but because the blood Wassermann reaction was negative. An endocrine hepatocardiac syndrome characterized by cirrhosis of the liver, pigmentation and infantile regression and followed by severe heart failure has been described. However, most of the characteristics of this syndrome were not present. Von Gierke's (glycogen-storage) disease must be mentioned. But this diagnosis seems unlikely when it is recalled that the patient was able to work as a truck driver until six months before admission to the hospital. Pericarditis with effusion is a possibility, and even the appearance of the heart in the x-ray film is not inconsistent with a considerable amount of fluid in the pericardium.

Nevertheless, I am led back to the original idea that in this case there was a myocarditis of essentially unknown origin that produced an extreme degree of cardiac enlargement, and that there may have been a mural thrombus, a portion of which broke away to cause cerebral embolism and death.

DR. WHITE: I came in contact with this case, having had correspondence with the patient's physician in another city, who spoke about the mystery of the illness and asked if we could take the patient for study. Although he lived only four days after arrival, we were able to make a satisfactory study; and he had been in the other hospital long enough to have even more complete studies.

Dr. Frank N. Wilson, of Ann Arbor, Michigan, was asked for an opinion. He wrote:

The story that you give in your letter is very peculiar and interesting. Complete heart block in young people is unusual. It is seen in congenital heart disease occasionally but almost always, if not always, in association with a defect in the ventricular septum and consequently with a systolic murmur that is loudest in the central part of the precordium. I have recently seen one case in which heart block may possibly have been due to myxedema, and it might be worth while to try the effect of desiccated thyroid. Syphilis of the myocardium, without definite evidence of involvement of the aorta, is extremely uncommon but does occur. It would be extremely unlikely in a man of twenty-one. Vitamin B<sub>1</sub> deficiency is said to cause very striking changes in the heart at times, but I do not believe that heart block has been reported. A severe deficiency of this type, with edema, is common, but there are neurologic changes. I take it that there is nothing in the history to suggest a deficiency disease. Marked enlargement of the heart may occur in sickle-cell anemia, which of course is, practically speaking, confined to Negroes, and in pituitary disease, particularly acromegaly. There does not seem to be any suggestion of this last condition here.

There is also a letter from Dr. Robert S. Starr, of Hartford, Connecticut, who had seen the patient. His final opinion was as follows:

It is doubtful whether congenital heart disease of any type could have been present throughout this boy's life without causing some degree of incapacity previous to the present illness. Moreover, the absence of murmurs and other objective evidence of congenital heart disease makes this diagnosis unlikely. Electrocardiograms, however, seem to indicate that the interventricular septum is rather particularly involved in the disease. The remarkable size of the heart by x-ray examination and the somewhat definite left ventricular and left auricular enlargement are noteworthy, but the symptoms so far have been chiefly those of failure of the right heart. Von Gierke's disease, although it must be considered, seems doubtful in the absence of a large liver.

I can add nothing except the note that I made on the ward the second day after admission.

Marked cardiac enlargement—dilatation and hypertrophy—with failure and extensive involvement of the auriculoventricular conduction system (complete heart block and left bundle branch block). A very bizarre syndrome at this age not fitting in with any ordinary cardiac diagnosis (rheumatic, congenital coronary or diphtheritic). It is possible, from the family history, x-ray findings and absence of other etiology, that rare neoplastic disease or von Gierke's (glycogen storage) disease may be responsible. It is not likely that we shall be able to establish an ante mortem (or perhaps even a post mortem) diagnosis.

#### CLINICAL DIAGNOSES

Congestive heart failure  
Von Gierke's disease

#### DR GRAYBIEL'S DIAGNOSES

Myocarditis, of unknown origin  
Complete auriculoventricular block, of congenital origin  
Cardiac enlargement, marked  
Congestive failure, marked  
Mural thrombi and cerebral embolism?  
Pericarditis, with effusion?  
Pulmonary embolism?

#### ANATOMICAL DIAGNOSES

Idiopathic hypertrophy and dilatation of the heart  
Mural thrombus, right auricle  
Pulmonary infarcts, multiple  
Anasarca  
Chronic passive congestion  
Thrombosis of posterior tibial veins

#### PATHOLOGICAL DISCUSSION

DR THOMAS B. MALLORY. Dr White's last statement is perfectly true. This man had an enormously dilated, moderately hypertrophied heart, one of the largest hearts from the point of view of capacity that we have ever seen, and all the chambers shared in the dilatation and in some degree of hypertrophy. The actual weight was

600 gm. The tricuspid valve measured 17 cm in circumference, the mitral between 13 and 14 cm. They are the two largest valve rings we have ever seen. The aortic and pulmonary valve rings, however, were quite normal. The coronary arteries were entirely normal. We made many microscopic sections of different areas of the myocardium, and none of them showed abnormality. The muscle fibers were somewhat larger than normal, but they showed no vacuoles of either glycogen or fat. There was not the slightest trace of inflammatory reaction to suggest myocarditis. The epicardium showed numerous petechial hemorrhages, which were found in various other spots in the body. It was noted that the blood had not clotted post mortem. Such failure of post-mortem clotting is suggestive evidence of an asphyxial death. There was a thrombus in the left auricular appendage, which could have been the source of five pulmonary infarcts that were found. On the other hand, the patient also had thrombosis of both posterior tibial veins, and I think that is the more probable source. Although there were several emboli, they had not produced large areas of infarction, and none of them were of sufficient size so that one could attribute death to pulmonary embolism. We made glycogen stains of various other organs, as well as of the heart, to be perfectly sure that we were not dealing with von Gierke's disease, and no abnormal deposits were found. The kidneys showed nothing that could not be explained by passive congestion.

DR DONALD S. KING. How about the shadow on the right side of the heart?

DR MALLORY. Perhaps that was one of the pulmonary infarcts.

DR WHITE. Each year, at the time of our graduate courses, we try to present one such case as this. It is not only very humbling, but it is also stimulating for our own further studies.

DR MALLORY. A year ago, an almost identical case<sup>1</sup> was presented, in older man, forty years of age, with marked hypertrophy and dilatation of the heart and absolutely nothing to explain the condition. Such cases have been reported in small numbers. Levy and Rousselot<sup>2</sup> reported 3 cases clinically similar, but 2 of these cases showed degenerative changes in the ventricular muscle.

A PHYSICIAN. There was no pulmonary endarteritis?

DR MALLORY. No.

#### REFERENCES

- 1 Case records of the Massachusetts General Hospital (Case 26401). *New Eng J Med* 223:54, 550, 1, 140.
- 2 Levy R. L. and Rousselot L. M. Cardiac hypertrophy of unknown etiology in young adults: a clinical and pathological study of three cases. *Am Heart J* 9:1-8, 192, 1933.

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established in 1828

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND  
PUBLISHED UNDER THE JURISDICTION OF THE COMMITTEE  
ON PUBLICATIONS

Official Organ of  
THE MASSACHUSETTS MEDICAL SOCIETY  
and  
THE NEW HAMPSHIRE MEDICAL SOCIETY

## EDITORIAL BOARD

Joseph Garland, M.D.	Stephen Rushmore, M.D.
William B. Breed, M.D.	Henry R. Viets, M.D.
George R. Minot, M.D.	Robert M. Green, M.D.
Frank H. Lahey, M.D.	Charles C. Lund, M.D.
Shields Warren, M.D.	John F. Fulton, M.D.
George L. Tobey, Jr., M.D.	A. Warren Stearns, M.D.
C. Guy Lane, M.D.	Dwight O'Hara, M.D.
William A. Rogers, M.D.	Chester S. Keefer, M.D.

## ASSOCIATE EDITORS

Thomas H. Lanman, M.D.	Donald Munro, M.D.
Henry Jackson, Jr., M.D.	

Walter P. Bowers, M.D., EDITOR EMERITUS  
Robert N. Nye, M.D., MANAGING EDITOR  
Clara D. Davies, ASSISTANT EDITOR

SUBSCRIPTION TERMS: \$6.00 per year in advance, postage paid, for the United States (medical students, \$3.50 per year); Canada, \$7.04 per year, Boston funds: \$8.52 per year for all foreign countries belonging to the Postal Union.

MATERIAL for early publication should be received not later than noon on Friday.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston, Massachusetts.

## PROCUREMENT AND ASSIGNMENT SERVICE

AN urgent call to all physicians to enter military service in the present emergency appeared in the January 1 issue of the *Journal*, as well as in the December 27 and January 3 issues of the *Journal of the American Medical Association*. The following statement by the Procurement and Assignment Service concerns the response of the medical profession and contains additional information that is of interest to those who, for one reason or another, cannot enlist in the United States Army or Navy:

The response of the physicians of the country to the Procurement and Assignment Service request for enrollment of those now ready for immediate service in the United States Army or Navy is highly gratifying. All names are being processed and those who meet the present demands of the Surgeons General will receive application forms and authority to appear for physical examination at an early date. All who are now ready for immediate duty should forward applications to the Procurement and Assignment Service at once. It is not the intention of the Procurement and Assignment Service to register every physician, dentist and veterinarian at the present time. Only those available for immediate assignments should register at this time. The physical requirements of all military, governmental, industrial, and civil agencies will be published in national and state journals immediately. On the basis of this information every physician, dentist and veterinarian will be able to make a self-appraisal of his physical qualifications. Within a few weeks the Procurement and Assignment Service will mail to all applicants a form on which they will be asked to state their preferences for assignment to all agencies of national defense which require medical, dental and veterinary personnel and for service in communities in public health and other civil categories. In this way every physician, dentist and veterinarian of the country will be able to lend maximum support to the national emergency. In order to meet the expanding needs of the military services, every physician immediately available for duty should mail his application blank to the Procurement and Assignment Service at once. All others will be given an opportunity to volunteer in the near future.

FRANK H. LAHEY, M.D., Chairman  
JAMES E. PAULLIN, M.D.  
HARVEY B. STONE, M.D.  
HAROLD S. DIEHL, M.D.  
C. WILLARD CAMALIER, D.D.S.  
SAM F. SEELEY, Major, M.C., U. S. Army  
Executive Officer

## UNITED WAR FUND CAMPAIGN

THE Greater Boston United War Fund Campaign, which begins on January 22 and will continue until February 11, represents a concerted endeavor on the part of the Greater Boston Community Fund, the American Red Cross, the United Service Organizations and the local Soldiers and Sailors Committee to raise \$7,600,000—nearly \$3,000,000 more than the goal of the Community

Fund last year. Boston is the only community of comparable size in which such a joint campaign is being conducted. Success therefore becomes a matter of civic pride and an example to other cities.

The campaign epitomizes the war effort of the Nation—the answer of free men to the threats of slaves and tyrants. For the money contributed, which will eventually have the effect of supporting the men in battle, is given voluntarily by those who wish to affirm their belief in the worth of liberty and justice. The American Red Cross sustains the morale of the armed forces in the field, distant outposts and hospitals by providing a link of communication between these men and their families; in addition, it must provide shelter, food, clothing and medical aid to the civilian victims of bombing, sabotage and other disasters. The United Service Organizations and the Soldiers and Sailors Committee direct their activities toward maintaining the morale of the service men. The Community Fund guards the vital home front: it protects the general population against poverty, sickness and despair—a trilogy that is potentially more menacing than armed invasion.

The war is on. Already, Pearl Harbor and Manila have become names to be remembered, names that mean temporary and honorable retreat before a treacherous, and therefore unexpected, assault. If the men who gave their lives in those battles are to be vindicated, every effort against the enemy must be supported. And the United War Fund Campaign represents such an effort.

The enormous goal can be attained only through the generosity of those who contribute. And this means sacrifice at a time when the burden of unprecedented taxation is becoming a reality. The quota of the Physicians' Group, \$37,415, is an increase of nearly 100 per cent over the total raised in last year's campaign. Physicians, accordingly, may well wonder how they can be expected to give such a sum: the number who are able to give contributions of several hundred dollars is decreasing; the doctor, like everyone

else, faces a discouraging rise in his tax rate; and many medical officers have already begun duty with the Army and Navy. The only solution is for *all* physicians to give. Those who have given before must be even more generous, and those who have not supported previous campaigns must contribute in proportion to what they have.

The United War Fund Campaign should be considered a call to arms for those who are being protected, after all, from the full shock of enemy attack. Moreover, the campaign is a challenge to all who prize their liberty sufficiently to fight for it. It is to be expected that physicians will be among the first to meet such a challenge.

## MEDICAL EPONYM

### MALPIGHIAN CORPUSCLES

"De internis glandulis renalibus, earum continuatione cum vasis [The Internal Glands of the Kidneys and Their Connection with the Blood Vessels]" is the title of the section of the discussion of the kidneys in which Marcello Malpighi (1628–1694), primarius in the Academy of Medicine at Messina, describes these structures. The quotation is taken from the edition of his *De viscerum structura exercitatio anatomica* [*Anatomical Essay on the Structure of the Viscera*], published at London in 1669, the first edition having been published at Bonn in 1666. A portion of the translation follows:

Since we have shown in a previous section that glands are found in the kidneys, and since, as will be shown below, these perform a special function in the excretion of the urine, it is advisable to spend a little time on them. They are located in the outermost part of the kidneys, are almost infinite in number, and probably correspond to the urinary vessels, which join to make up the main bulk of the kidneys. They are gathered into separate bundles, more than forty in number, and it is by virtue of these that those small divisions arise which appear in all kidneys. Wherefore, no definite description of their shape can be given on account of their minuteness and transparency, which is their chief characteristic: they seem, however, to be round like fish eggs, and while a black humor is passing through the arteries, they turn black; one might say that all round them they have shoots, moving like twining tendrils, so that they appear to be wreathed around, so to speak—with this exception, however, that the main part, which is fastened to the branch of the artery, turns black, whereas the rest retains its own color.

R. W. B.

## MASSACHUSETTS MEDICAL SOCIETY

## COMMITTEE ON MATERNAL WELFARE

ANALYSIS OF CAUSES OF MATERNAL DEATH IN MASSACHUSETTS DURING 1940 (*continued*)

## EMBOLISM

The immediate cause of death in 28 cases was embolism. Table 1 presents an analysis of these cases.

*After normal delivery.* A cerebral embolus occurred in 1 patient who was suffering from pulmonary tuberculosis. It was stated that she had only a short time to live in any event, and that the pregnancy had simply shortened her life. Three patients died after they had left the hospital—2 within twenty-four hours and 1 ten days later. It

TABLE 1. *Deaths due to Embolism.*

OCCURRENCE OF EMBOLUS	NO. OF DEATHS
After normal delivery	11
After operative delivery	7
After cesarean section	5
After abortion	2
During pernicious vomiting	1
During labor	1
After a separated placenta	1

is interesting that no serious pelvic operation preceded these embolic deaths. In 1 case, the patient delivered herself at about seven months; a few days after delivery, she was operated on for acute appendicitis and intestinal obstruction, and subsequently for a postoperative abscess. This patient died very suddenly just as she was leaving for home. The pregnancy may have obscured the diagnosis of appendicitis, because it was not definitely recognized until after delivery, although there had been symptoms preceding labor; this was a surgical death, but the immediate cause was embolism.

*After operative delivery.* In the 7 operative cases, 1 patient was delivered by version. She ran a febrile convalescence, and it is quite likely that an incomplete rupture of the uterus was sustained at the time of the delivery. One death occurred abruptly seven hours after delivery, and was undoubtedly due to embolism. One patient who was delivered by a low-forceps operation died the day after she arrived home; it was said that her convalescence had been entirely normal while she was in the hospital. Another patient developed an embolus three days after leaving the hospital and died abruptly. Another died on the ninth day, when she got out of bed. In 1 case, in which a low-forceps delivery was performed, the patient had an embolus about twenty minutes after de-

livery, and died four hours afterward. One patient, who developed respiratory embarrassment at the beginning of anesthesia, never recovered. Of course, it cannot be ruled out that the anesthetic was not the cause of this death, but the history suggests embolism. One patient delivered by low forceps developed respiratory embarrassment after 9 gr. of Nembutal and 1/150 gr. of scopolamine. The cyanosis was associated with much mucus and no vomiting; no anesthetic was given. This death was ascribed to embolism, although barbiturates may have really been responsible. The doses in this particular case were 3 gr. of Nembutal at 2:00 a.m. and 4 gr. at 6:00 a.m., with 1/150 gr. of scopolamine. About the only medical criticism in the treatment of these cases is that in the patients who left the hospital and died a few days after reaching home, phlebitis probably existed in each case and had not been diagnosed.

*After cesarean section.* There were 5 fatal cases of undoubted pulmonary embolism following cesarean section: 1 on the sixth day; 1 on the tenth day; 1 on the fifth day; 1 in a patient who was about to leave the hospital; and 1 four weeks following the operation as the patient was about to be discharged. The last patient had had an initial embolus at ten days. The number of deaths from embolism after cesarean section emphasizes the fact that fatal emboli are much commoner in cesarean sections than in normal deliveries. Embolism has always been recognized as a hazard of abdominal surgery, and because of this hazard, cesarean sections should never be entertained lightly.

*After abortion.* Miscarriage occurred in a patient one day after she had been operated on for acute appendicitis. Apparently, she was convalescing normally when suddenly, nine days later she went into a state of shock and died. One case of self-induced abortion was definitely septic. After she reached the hospital, this patient had been treated in the most approved manner—with transfusion, blood culture, no interference with the uterus and sulfanilamide therapy. Undoubtedly the embolus that caused her sudden death came from a thrombus in the pelvic veins. This case was turned over to a medical examiner, but no autopsy was performed.

*During pernicious vomiting.* In the case of pernicious vomiting, the patient died without operative interference. No attempt was made to interrupt the pregnancy, and it is probable that intravenous therapy had something to do with this death because the distress began three hours after intravenous glucose medication, and death occurred three minutes later. But, since this woman

was pregnant, the death was classified as a maternal death.

*During labor.* In a case of abnormal presentation, the patient died during labor. She was treated conservatively until full dilatation, and while being prepared for anesthesia, developed a severe pain in the chest and died within two minutes. In no way can the handling of this case be criticized. Unfortunately, an autopsy was not performed.

*After a separated placenta.* In the case of separated placenta, the patient was treated conservatively by cervical packing and an abdominal binder; although she had an anuria, which cleared up so that she passed 1200 cc. of urine on the ninth day, that evening she developed acute pain, cough and bloody sputum, and died eight hours later. One does not know how to prevent such a catastrophe.

\* \* \*

On the whole, a review of these deaths from embolism shows that most of them, in the present state of knowledge, are unavoidable. Patients who had been running slight fevers and died as they were about to leave the hospital, or a few days after they had returned to their homes, were not treated so conservatively as present knowledge teaches. It is possible that some of these cases might have been prevented had a diagnosis of phlebitis been made and had the vein at fault been operated on. This is a new branch of surgery, and at present only those who have had large experience in vein surgery should pass on each individual case. It has been suggested that heparin be used on operative deliveries when the element of trauma has been excessive. Since most of the cases of embolism were not associated with operative procedures, it seems as though the incidence following such procedure was not so great as it had been thought, and the cost of heparin therapy is still so prohibitive that any extensive research in the prevention of phlebitis and subsequent embolism by its use is out of the question.

## DEATHS

**BYRNES**—JOHN P. BYRNES, M.D., of Springfield, died recently. He was in his fifty-first year.

Dr. Byrnes received his degree from Albany Medical College in 1914. He was a former member of the Massachusetts Medical Society.

**HERSAM**—NORMAN P. HERSAM, M.D., of Stonham, died January 15. He was in his fifty-eighth year.

Dr. Hersam received his degree from Harvard Medical

School in 1912. He was a fellow of the Massachusetts Medical Society and the American Medical Association. His widow survives him.

## WAR ACTIVITIES

### EVACUATION SYSTEM MANUAL NO. 2

#### MEDICAL ORGANIZATION FOR PLAN A—EMERGENCY DISASTER

THIS IS THE SECOND MANUAL TO BE PUBLISHED RELATING TO CIVILIAN EVACUATION. ITS PURPOSE IS TO AID LOCAL SAFETY COMMITTEES IN ESTABLISHING ADEQUATE MEDICAL SERVICES IN CONNECTION WITH EVACUATION.

THE EVENT WHICH WILL MAKE AN EVACUATION OF THE CIVILIAN POPULATION NECESSARY WILL BE AN EVENT OF VIOLENCE. ITS INEVITABLE EFFECT UPON THE HUMAN BEINGS INVOLVED WILL BE THE DISRUPTION OF THEIR NORMAL CONDITION, BOTH PHYSICALLY AND MENTALLY: THE SHOCK, THE GRIEF, THE LOSS AND THE EXPOSURE WILL CREATE MANY MEDICAL PROBLEMS. THESE PROBLEMS MUST BE MET EFFICIENTLY AND PROMPTLY NOT ONLY FOR HUMANITARIAN REASONS BUT ALSO FOR REDUCING TO THE MINIMUM THE LOSS WHICH THE ENEMY SEEKS TO INFLICT.

J. H. SHERBURNE, *Director*  
Evacuation Division

Massachusetts Committee on Public Safety

Two previous publications dealing with civil evacuation have been issued by the Massachusetts Committee on Public Safety. *Bulletin No. 1: Evacuation of Civilians* considered the problem inherent in evacuation and gave information to be used in making evacuation plans. *Manual of Evacuation System, No. 1: Organization Plan A—Emergency Disaster* defined plans of evacuation to meet different types of emergency, described the organization to be developed and discussed the operation of these plans. The present manual is intended to describe the medical aspects of evacuation and the duties of evacuation medical officers. All evacuation medical officers should be thoroughly conversant with the previous publications.

*Bulletin No. 1: Evacuation of Civilians* was concerned with the removal of certain priority groups from danger zones to places of relative safety. Since its publication in June, 1941, the duties of the Evacuation Division have been broadened to include the evacuation and emergency care of all groups, except casualties, in the civilian population in the event of bombing or other war disasters. Obviously this is disaster relief, which is one of the major activities of the American Red Cross. It is therefore of the utmost importance that there exist the greatest co-operation between officers of the Medical Division, the Evacuation Division and the Red Cross, in order that there may be full utilization of all available resources. Red Cross facilities are to be augmented, not supplanted. It has been agreed between the Red Cross and the Evacuation Division that the former will supply, in so far as possible, ambulance service, mobile canteens, food, clothing, bedding, supplies and temporary shelter. Nursing care may also be provided, principally in the form of nurses aides. Medical personnel is furnished by the Evacuation Division.

*Manual of Evacuation System, No. 1: Organization Plan A—Emergency Disaster* defines five different types of evacuation. Plan A, the first to be worked out in detail, provides for the care and resettlement of civilians following an emergency disaster. Plans B, C, D and E probably

would be less hurried in their execution and would provide for resettlement on a long-term basis.

Civil evacuation will be voluntary except when compulsory evacuation is executed at the order of the military authorities or the government. The expense of evacuation will be met from public funds, but individuals cared for away from home will be expected to reimburse the government whenever possible for the cost of such care, either in whole or in part.

The specific objects of this Manual are as follows: to describe the duties of evacuation medical officers in the execution of Plan A; to describe the equipment and personnel needed; and to describe the various registration and examination forms and to discuss their use. Other manuals will be issued later in relation to Plans B, C, D and E.

#### ORGANIZATION AND DUTIES OF EVACUATION MEDICAL PERSONNEL

The organization of the Evacuation Division was described in *Manual of Evacuation System, No. 1: Organization Plan A—Emergency Disaster*. Its director will be assisted by a group of staff officers, among whom will be the chief evacuation medical officer and his deputy. It will be their duty to simplify, standardize and integrate all the medical activities of the Evacuation Division. They will be responsible for determining policies, outlining general plans and allocating evacuation medical facilities within the Commonwealth. They will send information to the regional evacuation medical officers and, through them, to the local communities. They will also maintain contact with the other divisions of the Committee on Public Safety, with the Red Cross, and with the Office of Civilian Defense for co-operative action between the states. They will have such advisory and liaison officers as are necessary.

Working under the state officers will be nine regional evacuation medical officers and their deputies. These officers will be called to duty at their regional headquarters in the event of an emergency. They will assist in every way the work of local evacuation medical officers. They should participate in the development of local evacuation facilities and arouse public interest in the work of the Evacuation Division. They control, through their district officers, all communications dealing with the medical aspects of evacuation between cities and towns in their regions. Communities needing additional medical assistance for evacuation should communicate with the regional evacuation medical officer and not with officers in adjoining localities. These might be equally affected by the disaster.

For each local evacuation officer, there will be appointed an evacuation medical officer and deputy, who will supervise the physicians, nurses and other personnel in their city or town who are working under the Evacuation Division.

An evacuation medical officer will be assigned to each report(control)-center area. He is the chief evacuation medical officer for that area, although there may be other evacuation medical officers working with him. One report center is usually organized for each 50,000 people in the State. It is the focal point from which all emergency service is rendered, and is controlled by the chief air-raid warden. Every evacuation medical officer should be thoroughly familiar with *Medical Handbook No. 2*, and also with the A.R.P. System. He should acquaint himself with all local facilities, especially those of the Red Cross, and should understand their organization. He should show the utmost co-operation in the use of these

facilities. He should know that supplies and equipment exist in fact as well as on paper. Personnel should be listed by address and telephone number, and should be fully acquainted with their duties. When the Red Cross or other agencies are not able to furnish nursing personnel, it shall be his responsibility to obtain nurses from other sources.

#### 1. Assembly Stations

Assembly stations will be selected in each community, their number and location depending on local conditions. They may be situated in buildings taken over for medical depots or may be identical in location with the casualty stations of the Medical Division. These assembly stations are under the direction of the Evacuation Division. The evacuation officer at the station will need the services of a physician, who will be provided by the Medical Division from their personnel present at the medical depot. He will be assigned to this duty by the chief medical officer at the report center. The medical officers of the Evacuation Division will not as a rule be called to duty until the temporary shelters have been selected. The chief evacuation medical officer should be sure that this arrangement is clearly understood.

It shall be the duty of the medical officer at an assembly station to reassure and calm any excited, worried or hysterical individuals—morale is of major importance and a competent individual can do much to keep it high—and to inspect all evacuees and treat any minor injuries or medical conditions that may be found.

In Appendix A will be found a list of the equipment needed at an assembly station. Arrangements have been made with the Medical Division to supply this kit and keep it filled. The chief evacuation medical officer is responsible for seeing that this equipment is kept at the medical depot and that supplies are replenished as necessary.

Any group of evacuees may include individuals subject to heart attacks, epileptic seizures and other medical emergencies, such as labor induced by the excitement of the occasion. To avoid confusion and therapeutic mistakes, each person receiving medical treatment will have this noted on an identification tag (the one used by the Medical Division), which should be attached to his person. In addition, a record must be kept of all medical treatment in a book provided for each unit. This must be returned daily to the chief medical officer at the report center at the end of each tour of duty.

#### 2. Transport

The medical officer at the assembly station will usually have no duties in connection with the transport of evacuees to temporary shelters, unless an urgent medical situation arises. The distances to temporary shelters will be short.

#### 3. Temporary Shelters

The medical officers of the Evacuation Division are responsible for medical care at the temporary shelters. As soon as the location of a temporary shelter has been selected, the chief evacuation officer will notify the chief evacuation medical officer who should at once go to the medical depot, collect his equipment and proceed to the temporary shelter. This chief evacuation medical officer will also call to duty sufficient nursing personnel. He will be responsible for the medical care of evacuees until the temporary shelter is cleared. Provision must be made for relief personnel, if necessary.

At the temporary shelter, considerable medical care

may be needed. The required equipment (Appendix B) will be supplied by the Medical Division. The chief evacuation medical officer is responsible for seeing that this equipment is on hand and kept in an appropriately labeled container at the medical depot. The evacuation medical officer will be responsible for having this kit brought to the temporary shelter when he goes on duty.

The medical personnel supplied to a shelter will vary according to the number of evacuees. There should, if possible, be at least one nurse for every one hundred evacuees, and aides should be supplied in the same ratio. Volunteers may be used for clerical help. All the facilities of the Red Cross will be needed, and should be used to the fullest extent.

All medical treatment must be recorded. If an identification tag was attached to the evacuee at the assembly station, the treatment should be noted on this tag, or if the evacuee is untagged, a tag should be attached and the entry should be made thereon. If, however, the evacuee has been registered, the entry can be made directly on the evacuation registration card (see below). All identification tags should eventually be removed and filed, and any entries made thereon should be copied on the evacuation registration card. A record of treatment must also be kept in the book provided with the medical kit.

Registration of evacuees by card will be done for administrative purposes and does not directly concern the medical officer. However, inasmuch as some persons will require emergency treatment, and since, under certain conditions, mass immunization may be necessary, space will be provided on these evacuation registration cards for medical information.

The chief evacuation medical officer or his deputy should be available to advise and consult with evacuation officers at information centers (see *Manual of Evacuation System, No. 1*) in the disposition of evacuees with medical or medicosocial problems. He should have a thorough knowledge of the Evacuation System, and should be conversant with the medical difficulties likely to be encountered in caring for children and persons handicapped by age or illness.

#### 4 Resettlement

Most of the evacuees will find permanent quarters for themselves and will need no medical examination other than the cursory inspection given at the assembly stations and temporary shelters. Those who have received some medical treatment should be given instructions concerning continuation of medical supervision, if necessary. There should be consultation with the Medical Division regarding facilities. A small percentage of the evacuees will require billing by the Evacuation Division. These persons will have a medical registration card and will receive a medical examination. So far as possible, evacuees will be housed in the locality, but they may be moved into another community, another region or, in the event of a major disaster, into another state. The chief evacuation medical officer at the place receiving them, wherever it may be, will act in accordance with procedures for a reception area, which will be considered in another manual.

For the medical registration of evacuees, cards of varying colors will be used, to permit rapid sorting by priority groups. The system will be as follows:

*White*—Healthy persons over fifteen years of age

*Blue*—Healthy children five to fifteen years of age

*Green*—Healthy children under five years of age

*Red*—Expectant mothers

*Orange*—Cripples, the aged and infirm, and handicapped individuals regardless of age

The term *healthy* is to be liberally interpreted. It should include individuals having slight handicaps, such as mild cardiac disease, malnutrition and other defects not limiting normal activities to any significant degree.

Such a system of classification will expedite the sorting of evacuees and aid in determining to what extent special medical facilities will be required. For example, plans will have to be made for the care of the aged in special homes, for the delivery of pregnant women in maternity hospitals and for the care and treatment of persons with such handicaps as blindness, crippling mental deficiency and convulsive disorders.

*Medical examination.* The medical registration card, which will go with the evacuee to the area in which he is resettled, should include a record of medical examination, which will be the beginning of a cumulative medical record.

Detailed and inclusive physical examinations do not seem necessary or feasible in view of the complexities and confusion of any evacuation and the possible shortage of medical personnel. The examination should be considered a rough screening process designed to eliminate individuals with contagious disease or serious handicaps. In children, the conditions most likely to be encountered are the exanthems, impetigo, pediculosis, scabies and, in young girls, vulvovaginitis. Adults should be inspected for the exanthems even though the probability of their contracting them would not be great. Examination for tuberculosis, syphilis and gonorrhea does not seem practical under these conditions.

Part of the medical inspection can be done by a nurse, leaving the physician to devote his time to the more important phases of the examination (about five minutes should be allowed) and to make final judgment in doubtful cases. Individuals over fifteen years of age should have a brief examination of the lungs and heart. Volunteer workers may be used for clerical assistance.

Evacuees who show signs of acute illness sufficient to make bed care necessary or who have developed any of the exanthems must be hospitalized. Arrangements for hospital and isolation facilities will require the co-operation of the Medical Division. If serious conditions are encountered, individuals should be sent by ambulance to the nearest hospital. Minor contagious conditions, such as impetigo, scabies and pediculosis, should not prevent the transportation of affected evacuees. If such individuals are to travel long distances in large groups, they should be segregated during their travels, and treatment should be begun as soon as they reach the reception area. In addition to the medical registration card, which will go with the evacuee to his final destination and there be kept in the custody of the chief evacuation medical officer, a travel tag indicating the evacuee's medical status, will be provided. This will facilitate the handling of mildly contagious evacuees. It will be attached to his person after he has undergone his medical examination.

*Transportation.* The transportation of evacuees will not be difficult when they are resettled locally. Except for the sick and the handicapped or for those in large urban centers many of them will be able to walk to their destination. However, evacuees may have to be moved in large groups and for a considerable distance, in which case more detailed plans will be necessary. Under these circumstances, as soon as evacuees have been registered and have passed the medical examination, they will be grouped and assigned to whatever buses, automobiles or trains may have been reserved for them. The evacuation officer in charge of each party shall be responsible for the



medical registration cards during transport, and shall deliver them to the chief evacuation medical officer at the resettlement area.

Healthy adult refugees will not need any more supervision in transit than would be provided by the transport officer in charge of the party, except when they travel in large groups. Healthy children from five to fifteen years of age will be adequately supervised by their school teachers or other individuals to whom this duty is delegated. More care will be required for young children, and medical supervision will usually be reserved for them and for handicapped evacuees. Special arrangements for such groups will be made by the local evacuation officer after consultation with his evacuation medical officer, his transport officer and any other interested parties.

It is assumed that each trainload or convoy of evacuees will at least be accompanied by persons who have had adequate Red Cross training and who have first-aid supplies to deal with minor emergencies.

If evacuees are transported distances requiring a traveling time of several hours, it is to be anticipated that medical emergencies will occasionally arise. Certain towns should be designated along the route where patients may be left in the hands of the local evacuation officer. If possible, he should be warned by telephone or telegram of his approaching responsibility, so that he may have time to make arrangements before the evacuee arrives.

If evacuees travel by auto or bus, they will probably arrive at the resettlement area directly. If, however, they go by rail, intermediate steps may be necessary before final billeting. Local evacuation medical officers must therefore arrange for certain medical facilities at disembarkation points. They and their aides should have armbands, uniforms or other distinguishing insignia. Equipment such as that described for assembly stations should be on hand.

This bulletin will not deal with the medical problems to be encountered in resettlement areas. It is obvious that long-term medical care of evacuees will require special planning. There will be time for epidemics of communicable disease to occur, and some control system must be set up. It may be necessary to arrange for clinic, hospital and domiciliary care of evacuees. The mental effects of bombing, separated families and strange surroundings will create new, and often disturbing, problems, especially among children. This phase of the evacuation process will be discussed in a later manual.

#### APPENDIX A. *First-Aid Equipment for an Assembly Station.*

- 6 pkg. Bandage compress, 3 in., 2 per pkg.
- 2 pkg. Tannic acid jelly
- 2 pkg. Gauze, absorbent, 1 yd. per pkg.
- 2 Bandages, gauze, 3 in.
- 4 Bandages, cravat triangle
- 48 Tags, identification
- 1 bot. Aromatic spirits of ammonia, 120 cc.
- 1 bot. Morphine sulfate, sterile solution, 20 cc., with rubber-diaphragm stopper (1 cc. contains  $\frac{1}{4}$  gr. morphine sulfate)
- 1 Syringe, Luer, 2 cc.
- 12 Needles, hypodermic, 24 gauge
- 1 bot. Alcohol, 90 per cent, 120 cc.
- 1 pkg. Nitroglycerin tablets, 100 per pkg.
- 1 pr. Scissors
- 1 pr. Tweezers
- 1 Pencil, indelible

- 1 Flashlight
- 1 box Throat sticks, 10 per box
- 1 Stethoscope
- 1 pkg. Drinking cups, paper
- 1 Book, record

These articles should be packed in a durable, clearly labeled container such as a haversack or suitcase.

#### APPENDIX B. *Medical Equipment for a Temporary Shelter.*

- 6 pkg. Bandage compress, 3 in., 2 per pkg.
- 2 pkg. Tannic acid jelly
- 2 pkg. Gauze, absorbent, 1 yd. per pkg.
- 2 Bandages, gauze, 3 in.
- 1 Gauze kit, Red Cross
- 4 Bandages, cravat triangle
- 1 lb. Cotton, absorbent
- 1 bot. Aromatic spirits of ammonia, 120 cc.
- 1 bot. Morphine sulfate, sterile solution, 20 cc., with rubber-diaphragm stopper (1 cc. contains  $\frac{1}{4}$  gr. morphine sulfate)
- 1 Syringe, Luer, 2 cc.
- 12 Needles, hypodermic, 24 gauge
- 1 bot. Alcohol, 90 per cent, 180 cc.
- 1 pkg. Nitroglycerin tablets, 100 per pkg.
- 1 pkg. Pentobarbital capsules,  $1\frac{1}{2}$  gr., 100 per pkg.
- 1 tube Vaseline, sterile, 45 cc.
- 1 pkg. Aspirin tablets, 5 gr., 100 per pkg.
- 1 bot. Suprarenalin solution (1:1000), 30 cc.
- 1 Catheter, urethral, rubber, No. 14 Fr.
- 1 Stethoscope
- 1 Flashlight
- 48 Tags, identification
- 1 pr. Scissors
- 1 pr. Tweezers
- 1 Pencil, indelible
- 2 boxes Throat sticks, 10 per box
- 1 box Safety pins
- 1 pkg. Drinking cups, paper
- 1 Book, record

These articles should be packed in a durable, clearly labeled container such as a suitcase or wooden box.

## MISCELLANY

### AMERICAN TRUDEAU SOCIETY

The diagnosis of clinically significant pulmonary tuberculosis is readily reached by the average practicing physician if certain fundamental procedures are used. One of the functions of the American Trudeau Society, the medical section of the National Tuberculosis Association, is to disseminate, among the general medical public, information about advances in these procedures. The treatment of tuberculosis in general is a specialized procedure, which should at least be initiated with the counsel of a specialist. The American Trudeau Society offers a forum where practitioner and specialist can meet to discuss the technical problems involved, as well as their practical application, and the following remarks of its president, Dr. Harold G. Trimble, are of interest.

\* \* \*

The American Trudeau Society is a natural outgrowth of the American Sanatorium Association, which was formed in the days when most of the medical problems of tuberculosis revolved around the various tuberculosis institutions and when many of the men in tuberculosis work

came by their interest because of their own personal history as tuberculosis patients. With increasing diagnostic facilities and with advances in various forms of treatment, general medical interest in diseases of the chest, including tuberculosis, was significantly increased and many young physicians became interested in these problems as such.

Theoretically, it seemed profitable, and practically it so developed, that contact between what one may call the pure specialist in tuberculosis and the internist, who although having other interests was intimately concerned with diseases of the chest, would benefit both. On this basis then with the co-operation of the National Tuberculosis Association the American Trudeau Society was formed—an organization of medical men with a nucleus of those interested primarily in tuberculosis and including a group interested in general internal medicine.

The idea of such a society, which would be inclusive rather than exclusive,—that is not confined to men who were primarily specialists in diseases of the chest—caught hold among the medical public, as evidenced by the rapid increase in members. Such an organization has a dual responsibility to push forward the already rapidly advancing knowledge of the technical medical as well as the public health aspects of tuberculosis, and to see that the known facts are disseminated even more rapidly among physicians in general. These functions are best achieved through the work of strong active committees with as wide a geographic distribution as possible and with a diversity of personnel to bring forth all aspects of the problem at hand. There are but few physicians of prominence in the field of tuberculosis or its closely allied specialties who are not active members of the American Trudeau Society. Members give generously of their time and information to work out special problems that may be referred to them or that they consider worthy of further investigation and study.

To provide information that is interesting, accurate and well thought through, to avoid mere novelties without overlooking new developments of intrinsic merit, and to review new phases of old problems is no mean task. This is the work of the Program Committee in arranging the annual meeting. If attendance is an index their efforts have been crowned with success.

As new techniques develop in the field of laboratory medicine in problems allied with diseases of the chest it is essential that the procedures be independently evaluated not by single individuals but by a group of physicians who are actively working in the same field and who have the facilities and personnel to try out the particular method without bias or undue enthusiasm. This is a task of the Committee on Standard Laboratory Procedures, and reports from this group are issued as promptly as possible.

Progress in the fields of diagnosis and treatment is based largely on technical developments in allied sciences. It is not always that these newer developments get to the medical student rapidly and effectively. The Committee on Undergraduate Medical Education, consisting of men who are experienced in teaching and alive to the needs of both student and medical school, is seeking more effective ways to reach this end.

The problem in postgraduate medical education is somewhat different. Practicing physicians are largely creatures of habit; they change but slowly techniques that they have learned and used so long. Only when something is really better, a distinct improvement and not merely different, will it be adopted. The purpose of the Committee on Postgraduate Medical Education is to make available as rapidly as possible knowledge of diagnostic

technics in the field of pulmonary disease particularly where it should be used the most, namely in the office of the physician in general practice. The realization that tuberculosis in its earliest stages when it is most curable, must be actually sought—since it is ordinarily without signs or symptoms—is still somewhat of a mental hazard for men who were taught years ago that fever, cough, sputum and so forth are indicative of tuberculosis, and that proper skill with the eyes, fingers and ears is adequate for diagnosis. As many new methods of using the x-ray become simplified more readily accessible and less expensive, the known facts regarding their effective use need to be widely disseminated. The committee is seeking to analyze the results of actual methods that have already been put into practical use and to get such information not to the tuberculosis specialist alone but particularly to the man in general practice.

New methods of x-ray procedure in the diagnosis of pulmonary conditions are in the course of rapid development. The Committee on X-ray Apparatus and Technique consists of men actively working in the application of x-rays to tuberculosis as a clinical problem as well as those working on technical improvement in existing apparatus. This group is in a position to evaluate the developments of the x-ray and to give this information to the members and the general medical public.

The tuberculosis sanatorium is and should be the focus around which the tuberculosis work of all kinds revolves. As the character of treatment changes, as more technical diagnostic procedures such as bronchoscopy, develop and as surgical collapse therapy grows in extent, there must necessarily be some alteration in the physical plant as well as in the type of medical care available for the tuberculous patient. The Committee on Tuberculosis Sanatorium Standards is now in the midst of evaluating these problems and will be able to report what is considered adequate current practice within the near future.

The policy of the American Trudeau Society, as originally adopted and reaffirmed on numerous occasions, has been that one seeking official certification as a specialist in tuberculosis should have a broad background in internal medicine. To that end the Society has a committee that co-operates with the American Board of Internal Medicine.

Thousands of professional workers, such as nurses, social workers and health officers, as well as many members of the general population, have served as board members of tuberculosis associations, on seal sale committees and in various other capacities. They have a real interest in the developments of technical problems in the field of tuberculosis. To give them authentic advice advisory committees have been set up for the purpose of reviewing such literature of the National Tuberculosis Association as is already available, as well as checking new publications as they are produced. The Committee on Educational Literature and the Committee on Medical Information must necessarily work in very close relation with these large groups of professional and lay persons interested in the general field of tuberculosis. This work to date has been effective, stimulating and productive of much good result.

This in outline, is the general philosophy and its practical application, of the American Trudeau Society. Its work covers those phases of the medical aspects of tuberculosis that are mostly problems for the specialists, as well as those that have special appeal to the physician in general practice. Its effectiveness can continue only so far as both these groups bring to it their current prob-

lems and, working through its committees, bring to bear jointly the sound advice and earnest counsel that is only theirs to give.—Reprinted from *Tuberculosis Abstracts*, January, 1942.

## CORRESPONDENCE

### TRAUMATIC EMPHYSEMA OF THE MEDIASTINUM

*To the Editor:* The clinical note in your number of May 29, by Dr. Gerald L. Gaudrault and Dr. Duncan M. Chalmers on the emergency treatment of traumatic emphysema of the mediastinum had an especial use and interest when read in England, which the march of events now spreads to include America.

In peace time, this condition is but rarely observed, and as a result it more usually receives post-mortem attention than emergency treatment. With the intensive bombing of cities and with the trapping of persons under debris, it is being brought to the notice of many practitioners who are not surgical specialists. It may interest you to learn that I have seen six such cases in one evening (this, even under raid conditions, was an unprecedentedly high figure), and in all the cases the picture was complicated by an intense venous congestion. The casualties had been sitting in the basement of a building built of brick and timber, which collapsed upon them, and when contact was made with them by tunnelling some three quarters of an hour after the bomb-fall, they were buried up to about waist level in brick debris, while the remains of a light concrete ceiling sheltered their heads and shoulders. There had been considerable debris pressure over the thoracic regions. Four of the individuals were dead, and two were moribund.

The two moribund patients showed intense cyanosis and venous congestion, marked dyspnoea, pulmonary oedema, and subcutaneous emphysema in the supraclavicular region and in the sternal notch. The condition in which they were found obviously prohibited a more scientific observation, and they died within some five minutes of being found and before they could be extricated.

It is probable that the condition of the cases described above was already too advanced to be benefited by surgical intervention, but it seems obvious that medical officers must be prepared in these days to carry out the procedures outlined by Drs. Gaudrault and Chalmers. A second point, not mentioned in their paper, and which might be considered, is the benefit accruing from venesection. The relief afforded to the heart and lungs would be undoubted, and the loss of blood and any increase of shock could be compensated for by transfusion at a later and more opportune moment.

The literature on this subject does not appear to be very rich, and in peace time, it seems that most of the experience of this condition would be afforded to surgeons dealing with mine accidents—to which air-raid casualties, seen from the point of view of an urban population, approximate. It would be interesting to learn what men with mine-disaster experience have to say.

K. W. C. SINCLAIR-LOUITT  
*Medical Officer for Civil Defence*

Finsbury Health Centre  
Pine Street  
London, E. C. 1

## REPORT OF MEETING

### HARVARD MEDICAL SOCIETY

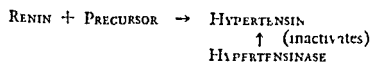
A regular meeting of the Harvard Medical Society was held at the Peter Bent Brigham Hospital on October 14, with Dr. James P. O'Hare presiding.

The case of a thirty-eight-year-old married woman who had entered the hospital six weeks previously because of pain in the right arm was presented. Her past history revealed no evidence of specific kidney disorder or scarlet fever. She was known to have had a negative urinalysis in 1922 while at a sanatorium for bronchiectasis. In 1927, during the seventh month of her first pregnancy, she began to show evidence of toxemia, which persisted until term. At that time, the urine showed a ++++ test for albumin and some erythrocytes, but there was no hypertension. In 1929, during a second pregnancy, she showed a trace of albumin at the fourth month and a phenolsulfonphthalein excretion of 45 per cent at the sixth month, and was delivered normally at term. There were similar findings of marked albuminuria without hypertension during two subsequent pregnancies, but apparent good health from 1935 to 1940. In 1940, the patient was found to have severe hypertension for the first time. During the previous year, there had been increasing fatigue and drowsiness, with frontal headaches, for six months, amenorrhea for five months, increased pigmentation and cramps in the extremities for three or four months and almost daily vomiting for two months. Physical examination revealed a dry, pigmented skin, exophthalmos, fundal hemorrhages without exudate, a normal heart, a blood pressure of 215 systolic, 130 diastolic, a nonprotein nitrogen of 121 mg. per 100 cc, marked albuminuria, and many erythrocytes and granular casts in the urinary sediment. On the tenth hospital day, the patient was given 500 cc. of compatible blood, with subsequent gross hematuria and a later increase in cellular casts in the sediment. Her course was one of increasing drowsiness, decreased vision, increased vomiting and an ever-increasing nonprotein nitrogen.

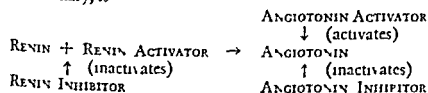
The case was discussed by Dr. Lewis Dexter, the speaker of the evening, who believed that this course of continued albuminuria, probably originating in the pregnancy, with no previous renal history, is neither common nor rare in a patient with cardiovascular renal disease. Post-toxicemic albuminuria or hypertension seems to be dependent more on the duration of this abnormality during pregnancy than on its severity, and any patient is prone to run fundamentally an albuminuric or hypertensive course until late in the disease. What causes the rather abrupt onset of hypertension after many years of albuminuria, as in this case, is difficult to explain.

The paper of the evening, "Some Recent Advances in Experimental Renal Hypertension," by Dr. Dexter, was a concise evaluation of progress in this field in the light of his own observations. He first discussed the humoral mechanism of experimental hypertension, which for practical purposes had its introduction in the work of Goldblatt and his collaborators, who, in 1934, reported that partial constriction of the renal artery in dogs resulted in prompt and chronic arterial hypertension. Subsequently it was demonstrated by various investigators that some humoral substances from the ischemic kidney must be a causative factor, since the same results were achieved in denervated kidneys and even in sympathectomized dogs. At present, the groups of Houssay, Braun-Menéndez, Fajano, Leloir and Muñoz, in Buenos Aires, and of Pa-

Corcoran, Helmer and Kohlstaedt in Indianapolis, are the foremost in attempting to elucidate this humoral mechanism. To corroborate the humoral aspect, Houssay and his co-workers grafted a kidney into the neck of an animal so that the circulating blood was the only connecting link, and demonstrated that, whereas a normal kidney only rarely caused a rise of blood pressure, an ischemic graft almost invariably did. He then analyzed the venous blood from normal and ischemic kidneys and found both a vasoconstrictor and a pressor substance in the latter. The active pressor substance was isolated and called hypertensionin, and was found to be identical chemically and pharmacologically with the pressor substance produced by the *in vitro* inoculation of renin and blood globulin. Renin had been found in kidneys as early as 1898 by Tigenstedt and Bergmann. Kohlstaedt, Helmer and Page, however, demonstrated that renin alone was incapable of a pressor action unless combined with a certain plasma globulin, which has been variously named precursor and renin activator. Apparently, renin is, or is similar to, a globulin of the enzyme class, and is liberated from the kidney as a result of renal ischemia. Precursor is the substrate, and the term renin activator seems to be a misnomer. This latter component is found only in blood, not in the bodily organs. Hypertensinase is another enzymatic globulin substance, found in practically all the bodily tissues, which acts quickly to inactivate hypertensionin. The Buenos Aires conception of the humoral mechanism of experimental hypertension is as follows:



Page and his co-workers began their investigations with purified renin and proved its inefficacy alone. They have reached essentially the same conclusions as Houssay and his collaborators regarding the nature of the reaction between renin and blood globulin (renin activator) to form a pressor substance (angiotonin), except that they postulate the presence of a so-called renin inhibitor and an angiotonin activator whose presence has not been clearly or unequivocally demonstrated. Their theory, in summary, is



Both the Indiana and Buenos Aires groups have demonstrated the presence of renin in the venous blood of ischemic kidneys. It is rarely present in demonstrable amounts in that of normal kidneys.

Among experiments on the role of amines in the pathogenesis of experimental hypertension may be mentioned the work of Bing on Dopa (dihydroxyphenylalanine). He has demonstrated that this substance is converted by decarboxylase (an enzyme found in renal tissue) under anaerobic conditions to a pressor amine that is probably dihydroxytyramine. Furthermore, its injection into an ischemic kidney results in a pressor effect not found when the same procedure is carried out in a normal kidney. No claim is made for an etiologic role, the ability of the kidney to produce pressor amines may eventually be found to be related to the renin blood globulin, hypertensionin or angiotonin reactions.

Dr Dexter then discussed the relation of experimental to human hypertension. Clinically, there have been at

least temporary cures of hypertension following removal of a unilaterally diseased kidney. Dogs made experimentally hypertensive run a course very similar to that of human beings. Several laboratory experiments, such as the isolation of renin from the human kidney, the changes in various clearance tests and the characteristic hypertensive response in animals to its injection further suggest a close correlation between the experimental and the clinical disease. But the results in one cannot justifiably be translated into those of the other.

Finally, there was a discussion of certain therapeutic agents that have been proposed and tried. An antibody against renin prepared by Wakerlin and Johnson by the repeated injection of pig renin into other animals, was reported to have controlled experimental hypertension. The work was corroborated by Prinzmetal. It is considered a promising lead. Secondly, renin extracts that have long been used therapeutically for hypertension have recently been studied intensively by Grollin in, Harrison and Williams, by Page, Helmer, and Kohlstaedt and by others. These extracts cause a temporary lowering of blood pressure in hypertensive animals and man as long as therapy is continued. Whether such extracts are specific or nonspecific in effect is not clear. It is known that the injection of many foreign proteins lowers blood pressure. In the reports, it is apparent that toxic reactions are sometimes noted when these extracts are injected or administered by mouth. The mechanism by which they lower blood pressure *in vivo* therefore, remains in doubt. *In vitro*, some of the extracts contain hypertensinase (angiotonin inhibitor) as well as renin. It is barely possible that the beneficial effects of the extracts lie in the production of Wakerlin and Johnson's antibodies to renin. Much more work must therefore be done to clarify the mechanism by which renal extracts lower blood pressure.

Tyrosinase, an enzyme that oxidizes phenols, has been studied by Schroeder and shown to cause a rapid fall of blood pressure in hypertensive animals and man. *In vitro*, there is claimed to be destruction of angiotonin. The results appear promising. Hypertensinase is still obtainable only in crude form but is efficacious in lowering the blood pressure of hypertensive animals.

Dr Otto Schales discussed certain enzymatic reactions in relation to that of renin and precursor and spoke in greater detail of the work of Bing and others regarding pressor amines.

Dr Robert W. Wilkins said that, on a recent visit to the Lilly Laboratory for Clinical Research in Indianapolis, he found Drs. Page, Corcoran, Kohlstaedt and Helmer engaged in studies on the depressor substance (angiotonin inhibitor) obtained from extracts of kidney. The administration of this substance to animals or to human beings with hypertension has often been followed by a dramatic lowering of the arterial pressure. At present, the Indianapolis workers are endeavoring to purify this substance, to eliminate toxic side reactions as well as to determine whether or not the presence of renin has anything to do with its action. They are convinced that its effect of lowering blood pressure is not the result of antibody formation. Studies of its physiologic effects show a reversal of the action of angiotonin—that is, an increase of cardiac output (ballistocardiographic) and an increase in renal blood flow with a decrease in the filtration fraction (Smith). Dr. Page and his co-workers are confident that this substance, when obtained in its pure state, will be helpful in lowering the arterial pressure of at least certain patients with hypertension.

Dr. F. A. Simeone reported on observations made during an attempt to obtain an animal for standardization of prospective therapeutic agents. The rapid accumulation of the responsible pressor substance was demonstrated by a hypertensive response as early as three minutes following clamping of the renal artery, with a maximum response in five minutes. The site of action was determined to be peripheral rather than cardiac by denervating the heart and carrying out adrenalectomy. That a multiplicity of substances emanating from an ischemic kidney may account for some of the variable and apparently controversial reports was suggested when some animals had lowering of the blood pressure to shock levels.

Dr. Alan Moritz suggested that, should an inhibitor or neutralizing substance be found, its role in many cases would simulate that of insulin in diabetes, for the irreversible kidney changes would require constant therapy to maintain the status quo.

In reply to a question concerning the role of desoxycorticosterone in the present conception of the etiology of hypertension, Dr. Dexter stated that this hormone is now known to be effective in the hypotension of Addison's disease. Furthermore, after adrenalectomy in dogs, there is sometimes a fall in the concentration of precursor in the plasma. The injection of several of the sex hormones has been reported to elevate the blood pressure of normal animals. The exact relation of the adrenal cortex to blood pressure is, however, far from complete.

## BOOK REVIEWS

*Abnormal Speech.* By E. J. Boome, M.B., Ch.B., M.R.C.P., D.P.H., T.D., and D. G. Harries. 12°, cloth, 162 pp. Cleveland, Ohio: The Sherwood Press, 1939. \$2.50.

The authors present in rather readable style the results of their combined experience with speech disorders. They divide such disorders into three types: the functional disorders of speech, which they consider to be due to imperfect perception of speech or control of the process of utterance in spite of normal organs of speech; the organic disorders of speech caused by malformations, diseases and so forth; and the psychogenic disorders of speech due to nervous disorders. It is difficult to ascertain what the authors mean by nervous disorders. Among the functional defects are delayed speech, lalling, lisping, cluttering and such conditions as aphasia and disorders of phonation that one would expect to find usually when organic disease is present. Among organic defects are considered deafness, palatal defects and dental irregularities. The chief nervous disturbance affecting speech is considered to be stammering. The authors also include a neurotic lisp, a lateral lisp and voluntary mutism as psychogenic disorders.

Throughout the discussion, one meets expressions that are difficult to interpret, particularly those dealing with energy and brain function, in which a tense or sluggish brain producing an unrhythmic movement is described.

Regarding therapy, the authors suggest all sense-training exercises and some motor exercises to help the functional defects. The remedy of organic defects depends on the nature of the defect. The psychogenic disorders are apparently to be helped through exercises for relaxation in which the authors place a great deal of faith. Such exercises are described in detail. Following this survey of abnormal speech, there are chapters on the mentally defective child and his speech and on the "difficult" child and his speech, and a final review of recent progress in speech therapy.

The book is written for use in England, reference being made to the various dialects of that country, and its chief value to an American reader is to serve as a means of being posted on what some workers in the field of speech disorders are doing in another country.

*The 1940 Year Book of Public Health.* Edited by J. C. Geiger, M.D., Dr.P.H. 12°, cloth, 560 pp., with 12 figures and 24 tables. Chicago: Year Book Publishers, 1940.

This is the usual digest of current articles dealing with public health; it is noteworthy that more and more activities are coming within the circle over which the professional public-health worker casts his eye. More than four hundred articles are abstracted, and editorial comments are frequently interpolated. This is the first time that the Year Book Publishers have printed a volume on public health. The result is admirable for those whose particular interests do not lie within the larger field of medicine or for those whose interests are concentrated into smaller fields. The public-health worker himself will probably be better served by the original sources, if he has the time to peruse them. If he has not, he, too, can get a sense of proportion from this reading method.

*Foundations of Neuropsychiatry.* By Stanley Cobb, M.D. Second revised and enlarged edition of the work formerly known as *A Preface to Nervous Disease*. 8°, cloth, 222 pp., with 12 illustrations and 3 tables. Baltimore: Williams and Wilkins Company, 1941. \$2.50.

Because the second edition of this book is based largely on neuropathology, the author has changed the title to fit his material. In addition, he has revised much of the work and slightly enlarged the book. Parts have been rewritten, and in general, the book has been greatly improved. It now forms the best study of its type in English, and should be put in the hands of every medical student. Moreover, the volume will interest a good many thoughtful physicians and will be of particular value to specialists in neurology and psychiatry. The most important addition is the section on psychopathology, which lists the main syndromes of psychiatry. In this short chapter, the author has put a large amount of material in an abbreviated but clear manner. Seldom has the reviewer seen a second edition of a book so vastly improved. Apparently, the author has read the constructive criticisms incorporated in the reviews of the previous edition.

*America Organizes Medicine.* By Michael M. Davis. 8° cloth, 335 pp. New York and London: Harper and Brothers, Publishers, 1941. \$3.00.

This is a thorough and excellent presentation of the relations between a changing medical profession and a changing social order. The points of contact and conflict are discussed in a way that, in the words of the author, "will not satisfy partisans but may promote thought that will diminish partisanship." The weakness of the book is that it presents the point of view of a social worker. For example, it is stated that it is profitable for the optician to turn over a portion of the sale price of eyeglasses to the physician who sent the patient—"This practice is said to be widespread." A medical collaborator would also have mentioned the much greater evil of selling eyeglasses to people who do not need them. The author is more sensitized to the economic aspect of the situation than he is to the physiologic, but his book is nevertheless a helpful discussion.

(Notices on page x)

# The New England Journal of Medicine

Copyright, 1942, by the Massachusetts Medical Society

VOLUME 226

JANUARY 29, 1942

NUMBER 5

## CANCER OF THE BREAST

### Results of Surgical Treatment at the Collis P. Huntington Memorial Hospital

CHANNING C. SIMMONS, M.D.\*

BOSTON

THIS paper is a report of the results of the surgical treatment of 135 cases of cancer of the breast observed at the Collis P. Huntington Memorial Hospital up to 1936. It has been made for comparison with several similar reports of cases treated and analyzed in approximately the same manner at the Massachusetts General Hospital.<sup>1-6</sup> The surgery was done by practically the same group of men in both series, or under their guidance. The series is small, but in the earlier years, little major surgery was done at the Huntington Hospital, with the exception of special cases in which the study of new methods of treatment was being made, the patients who required surgical treatment being referred to the Massachusetts General Hospital. Although approximately 100 cases of cancer of the breast are seen in a year in the clinic, the majority are patients with advanced or recurrent disease in whom surgery is contraindicated.

It is somewhat difficult to report this series in a manner that allows comparison with those reported by other observers. The cases have been followed from five to nineteen years. If the results are reported on a strictly five-year basis, as many results are, the percentage of successful cases is much higher than that given here.

The same criterion for operability was employed in this as in the other series mentioned, namely, that the disease must be confined to the breast or the breast and axilla. The presence of obvious involvement of the lymph nodes above the clavicle or of remote metastases rendered the case incurable by surgery. X-ray films were taken of the bones and lungs before operation, to exclude the presence of remote metastases. If remote metastases were found, it was believed that the disease was incurable and that the local tumor could be

held under control by radiation treatment during the patient's life. In a few of the incurable cases, if by simple amputation the growth could be removed with sufficient tissue to render immediate local recurrence improbable, the operation was justified in patients who would rather be rid of an obvious tumor than be continually conscious of its presence and have to report for treatment.

Among the 155 patients who were operated on there were 2 men, an incidence of 1.3 per cent. One of these patients died of another cause in less

TABLE 1. *Analysis of Cases.*

	No. of Cases
Total number of patients	155
Disease limited to breast	55 (34%)
Axilla involved	100 (66%)
Operative deaths	3 (1.9%)
Inconclusive deaths (deaths from other causes in less than five years)	20
Cases available for end result study	135

than five years, and the other is living with recurrence eight years after operation.

In the subsequent discussion, radical operation is considered to be the removal of the entire breast with a large amount of skin and subcutaneous tissue, together with both pectoral muscles and the contents of the axilla.<sup>7</sup>

The term "cure" is applied to patients living without evidence of disease at the time of last examination and at least five years after operation. Those who died postoperatively are considered "dead of disease." This may not be quite accurate, but it makes little difference to the patient whether he dies of disease or as the result of operation. The 20 patients who died of another cause without disease less than five years from the date of operation are excluded as inconclusive in determining the end results (Table 1).

\*Consulting surgeon, Massachusetts General Hospital

There were 3 postoperative deaths among the total of 155 patients who were operated on,—2 due to pulmonary embolism and 1 to sepsis and shock,—the mortality being 1.9 per cent. It is interesting to note that, in one of the patients who died of pulmonary embolism, the source of the embolus at autopsy was found to be the iliac and not the axillary vein.

The 135 cases suitable for study of the end results again have to be divided, possibly arbitrarily, but in a small group classed as "palliative" the operations were performed usually in conjunction with radiation treatment and with no hope of cure by surgery alone. It does not therefore seem fair to include them with a group in which surgical cure was considered possible. A second group, "incomplete operations," composed of elderly people on whom a simple amputation was done, usually under local anesthesia, to remove a tumor apparently confined to the breast, is also considered separately.

RADICAL OPERATIONS

Excluding the groups with palliative and incomplete operations, there were 116 cases in which a radical attempt at surgical cure was made, with cure of from five to nineteen years in 50 cases (42 per cent). In the group in which the axilla

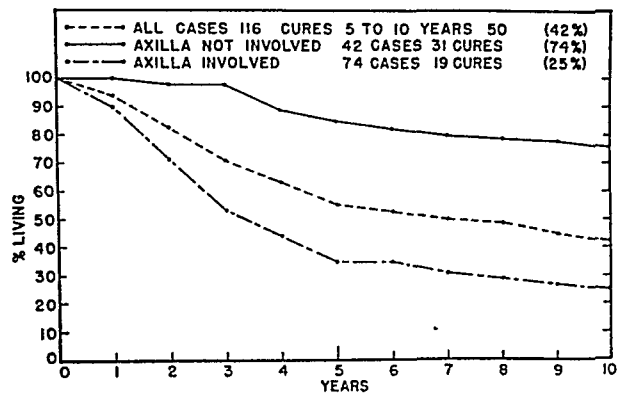


FIGURE 1. Results of Radical Operation for Cancer of the Breast.

was not involved (42 cases), there were cures in 31 cases (74 per cent), and in those with involvement of the axillary lymph nodes (74 cases), there were cures in 19 cases (25 per cent). These figures correspond closely to those reported in the last two series from the Massachusetts General Hospital: namely, 1927 to 1929, 43 per cent, and 1930 to 1932, 45 per cent. The percentage of cures at yearly intervals is shown in Figure 1.

For comparison with the figures reported by other observers on a strictly five-year basis, the cures by surgery alone in the entire group are 55

per cent, and in cases without axillary involvement, 85 per cent (Table 2). The latter group, however, includes cases cured by simple amputation in which the result indicates that the axilla

TABLE 2. Comparison of Results after Five Years and Over.

TYPE OF CASE	CURE AT 5 Yr.	CURE AT 5-19 Yr.
	%	%
All cases	55	42
Cases without axillary involvement	85	74
Cases with axillary involvement	35	25

was not involved. No patient in whom the lymph nodes were uninvolved developed recurrence after five years.

The number of cases of late recurrence is impressive (Table 2). I believe that the percentage

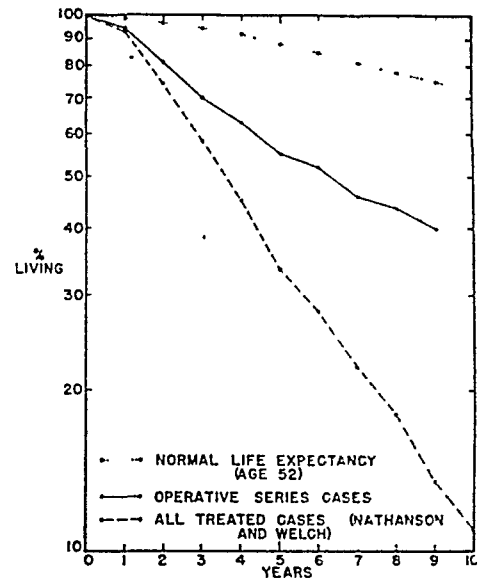


FIGURE 2. Logarithmic Chart Showing Survival Rates for Patients with Cancer of the Breast.

of cures would be much lower if all cases had been followed for ten years. Formerly, it was estimated that 15 per cent of patients living without evidence of disease at the end of five years would eventually die of recurrence, but in this series the percentage is larger: thus, of 20 patients living at the end of eight years, 7 eventually died of metastases. It is only fair to state, however, that 4 of these presented recurrence at an earlier date and lived with known disease four, five, six and seven years respectively, 1 eventually being killed in an automobile accident. This group emphasizes the vagaries of the disease and the difficulty of evaluating any form of treatment.

The cases have been plotted on a logarithmic chart (Fig. 2), which allows for the number of patients followed for varying lengths of time and the numbers dying of disease yearly. On this chart.

there is a constant percentage of deaths up to ten years. The dotted line represents the life expectancy of all women after the age of fifty-two. The solid line indicates the yearly survivals of the cases of cancer of the breast; it includes only those who died of the disease. The broken line, from Nathanson and Welch,<sup>8</sup> represents the expectation of life in patients with cancer of the breast who have received some form of treatment. The report of Daland,<sup>9</sup> who followed 100 untreated cases of *cancer of the breast and found that 26 per cent were living at the end of five years*, should also be borne in mind in estimating the value of any method of treatment.

This series is of course small, and it would be interesting to follow a large group for from ten to fifteen years, but the difficulty of doing this accurately is practically insuperable. The figures imply, however, that a patient with cancer of the breast cannot be considered as certainly cured even though living without evidence of disease five years after operation. On the other hand, no patient in whom the disease was limited to the breast developed recurrence after the fifth year.

#### *Effect of Duration of Disease before Operation on End Results*

The median duration in cases in which the disease was limited to the breast was two months, and in those with positive axillary nodes, nine months. The average duration in these two groups was six and nine months respectively. The median duration gives a much more accurate picture of the effect of delay on the extent of the disease and the possibility of cure than the average duration, for if the latter figure is employed, one or two cases of very long duration will influence the figures and give an erroneous impression. The figures given are essentially the same as those reported in the publications previously referred to.

The delay of adequate treatment is usually due to the patient. So far as could be determined, 19 patients received poor advice from the first physician consulted. This is discouraging, considering the amount of educational work that has been carried on in Massachusetts by the Department of Public Health for the last fifteen years. When the delay, or duration of disease, was compared with the degree of malignancy as determined by the pathological examination of the specimen, it was found that in 33 per cent of cases of low malignancy, 38 per cent of medium malignancy and 54 per cent of high malignancy, the patient sought advice within three months. This may be interpreted to mean that a rapidly growing tumor at-

tains a size that causes concern to the patient more quickly than one of low malignancy.

#### *Effect of Extent of Disease on End Results*

The extent of the disease, that is, whether it is limited to the breast or has extended to the axillary lymph nodes, is apparently the most vital factor in the prognosis. In 36 per cent of the cases, the axillary lymph nodes showed no evidence of disease on pathological examination, and 74 per cent of these patients were cured for from five to eight years; if a strict five-year limit is employed, the cures were 85 per cent. In 66 per cent, the axillary nodes were involved, and the percentage of cures was 25. Unfortunately, the extent of the lymph-node involvement is not stated in the pathological reports; 35 per cent of patients, however, were living without evidence of disease at the end of five years. Of the patients living at the end of five years, 22 per cent eventually died of disease. Since many patients have not been followed for much over five years, it is probable that many now living, apparently free of disease, will eventually develop recurrence. As has been previously mentioned, no patient with uninvolved axillary lymph nodes developed recurrence after five years.

A study has been made to determine the value of physical examination in estimating the extent of axillary involvement. In 59 cases in which it was stated in the record that no axillary lymph nodes could be felt, cancer was found in 25, representing a 40 per cent error. When the nodes were palpable, 80 per cent later proved to be cancerous. The evaluation of the extent of the disease by clinical means alone is therefore subject to considerable error.

#### *Effect of Degree of Malignancy on End Results*

In previous communications, all tumors have been graded pathologically into three degrees or grades of malignancy,—low, medium and high,—depending on the degree of differentiation of the cells, as suggested by Broders<sup>10</sup> in 1920; it was found that, with the exception of the extent of the disease, this was the most important factor in the prognosis. In a few cases in this series, specimens were not available for review, but the relation of the index of malignancy to the results has not worked out as in previous analyses. The largest number of cures occurred in the cases of low malignancy, but there was a greater percentage of cures in tumors of high than in those of medium malignancy. The results are shown in Table 3.

It should be noted that in no tumors of low malignancy (10 cases) were the lymph nodes diseased, and that all the patients were cured. Three



other cures were obtained by simple amputation in cases of low malignancy.

In 6 cases, the cancer arose from a papillary cystadenoma, and the axilla was not involved; 5 of these were of low malignancy and 1 of high, and all the patients were over fifty years old.

Cancer was associated with Paget's disease of the nipple in 5 cases, in 3 of which the nodes were

TABLE 3. *Relation of Malignancy to Cure.*

DEGREE OF MALIGNANCY	ALL CASES		CASES WITHOUT INVOLVED NODES		CASES WITH INVOLVED NODES	
	NO.	CURES %	NO.	CURES %	NO.	CURES %
Grade 1	10	100	10	100	None	—
Grade 2	72	38	24	54	48	30
Grade 3	24	50	8	100	16	25

involved; in 1 of these, the patient was cured. The 2 patients without axillary involvement are well.

Seven cases were classed as colloid cancer, 4 of which are suitable for end-result studies. In 3, the nodes showed disease, and the patients are dead. The patient with uninvolved nodes is living.

Three cases of so-called "inflammatory cancer," all in relatively young women, were considered incurable by surgery alone when first seen. Some form of surgery was employed, however, in conjunction with radiation treatment; all the patients are dead.

#### *Effect of Age on End Results*

It has often been stated that the prognosis of cancer of the breast is much worse in women under forty than in elderly women. The groups of cases from the Massachusetts General Hospital have always failed to prove this except in the last series analyzed, in which, however, it was shown that the prognosis really depended on the degree of malignancy and not on the age of the patient.<sup>6</sup> The present group, although small, confirms the previous findings, since the age of the patient had little relation to the end result.<sup>11</sup> Of 16 patients under forty years of age, 10 are living and 6 are dead, whereas in 19 cases over sixty, 10 are living and 9 are dead. In the younger group of the patients living, the disease in every case was confined to the breast, but in only 3 was the tumor graded as of low malignancy. In the elderly group, 5 of those living showed tumors of low malignancy, and 5 cases were of higher grades of malignancy, in which 3 showed axillary involvement.

#### *Effect of Biopsy on End Results*

A biopsy at the time of operation to verify the clinical diagnosis was performed in 28 (25 per cent) of the cases. Fifty per cent of this group

of patients are well. The results are slightly better than those of the full series, as would be expected, for biopsy was performed only when the clinical diagnosis was questionable. In 26 per cent of these cases, the disease was later found to be limited to the breast, and in the remainder the lymph nodes were involved. This illustrates the difficulty of making a correct clinical diagnosis even in the presence of relatively extensive disease. In the two groups, with or without lymph-node involvement, the comparative results were similar to those in the general series in which no biopsy was performed.

To obtain a specimen, it has been the practice to make an incision directly into the tumor, and if it proves to be cancer, the wound is packed with formalin gauze and closed before the radical operation is performed. Removal of a specimen for diagnosis under local anesthesia and performing the radical operation at a later date is considered a dangerous procedure, for although it is difficult to obtain definite statistical evidence, it is believed that the results are not so satisfactory as those when the biopsy is followed immediately by radical operation. In most cases, the diagnosis is obvious when the tumor is incised.

#### *Site of Recurrence*

The principal site of recurrence was known in 67 of the patients dying of disease, although in most cases the recurrences were multiple. In 95 per cent of the entire group, there was a local recurrence. The commonest remote sites were in the bones or lungs (23 per cent each), although practically every organ of the body was diseased in some patients.

The 14 cases in which recurrence was late, that is, after five years, are of particular interest. In 4, the disease had been limited to the breast, and the recurrence was remote; there was evidence of recurrent disease before the fifth year, however. One patient showed evidence of disease of the lung five years after operation but lived for seven years, or twelve years from the date of operation. Of the 10 patients with involved lymph nodes who died of late recurrence, local recurrence appeared at the end of six years in 2, and in 8 the recurrence was remote; 5 of the latter lived for nine years or more. There was no demonstrable relation between the extent of the disease, the degree of malignancy or the age of the patient and the development of late recurrence.

#### PALLIATIVE OPERATIONS

All the 9 patients in this group showed extensive disease or presented rapidly growing tumors,

and were considered incurable by surgery alone. Radical operation was done as a supplement to radiation treatment. Three were cases of what may be called "inflammatory carcinoma." Of this group, 1 patient died as a result of operation, and the other 2 died of the disease.

#### INCOMPLETE OPERATIONS

Of the 10 patients in whom amputation of the breast without dissection of the axilla was performed, 4 were living without disease five or more years after operation. All were poor surgical risks, and in 6 the operation was performed under local anesthesia. At first glance, these results are as favorable as those following radical operation, but in a study of the cures, 3 cases had tumors of low malignancy that arose in papillary cystadenomas, and in 1 case the tumor was small. In no case were the lymph nodes involved, and the 40 per cent cures should be compared with the 74 per cent cures following radical operation in the same group.

#### IRRADIATION

The general policy of the hospital has been not to employ radiation treatment before operation or as a postoperative measure unless the disease was more extensive than had been anticipated and there was a possibility that tumor tissue had been left in the axilla. The rationale of preoperative irradiation to inhibit the growth of cells is understandable but I do not believe that the results following operation on a tumor that at one time was considered inoperable but has diminished in size following irradiation will be satisfactory except in an occasional case.

If a sufficient dosage of postoperative irradiation is given to destroy cancer cells, permanent damage to the skin may follow, and small doses do not accomplish results. Furthermore, it is difficult to see how recurrences can be affected by irradiation of the chest, for in only 9.4 per cent of the cases were they local—the figures from the Massachusetts General Hospital series show 7.5 per cent local recurrence. In recurrent cancer, however, radiation treatment applied to the lesion is of great value.

In this series, postoperative irradiation was employed in 2 cases without axillary involvement; both patients are well. It was also employed in 11 patients with involvement of the axillary lymph nodes, 3 of whom are well. These figures are approximately the same as those for the entire group. In 13 cases, an artificial menopause was brought about by irradiation. In 5 of these, the disease was limited to the breast, and 4 patients

were under forty years of age—these 4 are living without disease. In 8 patients, the lymph nodes were involved, and 3 of these are living. This is a small group, but the figures vary but little from those of the entire series.

An attempt has been made to study and tabulate the results of treatment of the advanced cases by irradiation; although definite impressions have been obtained of its value in inoperable and recurrent cases, it is impossible to make any rules for treatment or to report fairly the results. In practically all, symptomatic and temporary relief was obtained, but when the vagaries in the course of the disease are considered, it is very questionable if life was actually prolonged, and certainly there have been no cures.

#### SUMMARY AND CONCLUSIONS

The results of the surgical treatment of 135 cases of cancer of the breast at the Collis P. Huntington Hospital are reported. The end result is known in every case, and all surviving cases have been followed from five to nineteen years.

One hundred and sixteen of the patients underwent radical operations. Forty-two per cent of them were living without evidence of disease five or more years after operation. In the cases in which the disease was confined to the breast, there were 74 per cent cures, and in those showing involvement of the axillary nodes, 25 per cent. On a strictly five-year basis, the cures were 55 per cent for the series, 85 per cent for the cases without axillary disease, and 35 per cent for those with involvement of the lymph nodes. The most significant factor in the prognosis is therefore the extent of disease.

The pathological index of malignancy is probably, next to the extent of disease, the most important factor in the prognosis, although the figures in this series are not so conclusive as those of others; however, it is admittedly more difficult to grade an adenomatous than a squamous-cell tumor.

Of the 64 patients apparently well at the end of five years, 14 (22 per cent, or 12 per cent of the entire group) died later of recurrence. Of 20 patients living over eight years, 7 eventually died of cancer. Because many of the cases were not followed for more than five or six years, it is probable that some of these will develop a late recurrence. On the other hand, the 4 patients without axillary involvement who died of disease after five years all presented evidence of metastases before the fifth year. It therefore appears that patients in whom the axillary lymph nodes are not involved and

who show no evidence of recurrence within five years may be considered permanent cures.

The age of the patient in itself has no relation to the curability.

Recurrence in the operative field in suitably selected cases is relatively rare.

205 Beacon Street

## REFERENCES

1. Greenough, R. B., Simmons, C. C., and Barney, J. D. The results of operations for cancer of the breast at the Massachusetts General Hospital from 1894 to 1904. *Surg., Gynec. & Obst.* 5:39-50, 1907.
2. Greenough, R. B., and Simmons, C. C. End-results in cancer cases: cancer of the breast. *Boston M. & S. J.* 185:253-261, 1921.
3. Greenough, R. B., and Taylor, G. W. Cancer of the breast: end-results. Massachusetts General Hospital 1921, 1922, and 1923. *New Eng. J. Med.* 210:831-835, 1934.
4. Simmons, C. C., Taylor, G. W., and Adams, H. B. Cancer of the breast: end-results, Massachusetts General Hospital, 1927, 1928 and 1929. *New Eng. J. Med.* 215:521-525, 1936.
5. Simmons, C. C., Taylor, G. W., and Wallace, R. H. Cancer of the breast: end-results: Massachusetts General Hospital 1924, 1925, and 1926. *New Eng. J. Med.* 210:836-844, 1934.
6. Simmons, C. C., Taylor, G. W., and Welch, C. E. Carcinoma of the breast: end-results. Massachusetts General Hospital, 1930, 1931, and 1932. *Surg., Gynec. & Obst.* 69:171-177, 1939.
7. Taylor, G. W., and Daland, E. M. The Greenough technique of radical mastectomy. *Surg., Gynec. & Obst.* 65:807-811, 1937.
8. Nathanson, I. T., and Welch, C. E. Life expectancy and incidence of malignant disease. I. Carcinoma of the breast. *Am. J. Cancer* 28:40-53, 1936.
9. Daland, E. M. Untreated cancer of the breast. *Surg., Gynec. & Obst.* 44:264-268, 1927.
10. Broders, A. C. Squamous-cell epithelioma of the lip. *J. A. M. A.* 74:656, 1920.
11. Taylor, G. W. Carcinoma of the breast in young women. *New Eng. J. Med.* 215:1276-1278, 1936.

## PSYCHIATRIC ASPECTS OF ULCERATIVE COLITIS\*

GEORGE E. DANIELS, M.D.†

NEW YORK CITY

A RECURRENT, wasting and often fatal disease with no established etiology presents a challenge on all medical fronts. So far, attempts to prove that a specific organism is the primary cause of ulcerative colitis have failed. General skepticism concerning the efficacy of the numerous medical procedures extant serves to emphasize the stalemate that has attended progress in the basic knowledge and treatment of this disease. Surgery is generally reserved for cases in which conservative measures have failed; the mortality rate is high after surgical intervention, and a successful operation generally leaves the patient with the annoyance of a permanent colostomy.

Sometimes, an entirely new approach reveals surprising results in such a situation, and this can truly be said to have occurred when a psychiatric approach was applied to the study of what is commonly known as nonspecific, or idiopathic, ulcerative colitis. The few authors who have thoroughly investigated the subject consider that emotional conflict furnishes the most consistently recurring factor. The degree to which it may supply the missing etiology in a large group of cases still remains to be proved. It is not my purpose to attempt such proof, but to present a few facts that may be of general use to the practitioner.

Ulcerative colitis appears in a fulminating form that runs a few weeks and is often entirely resistant to treatment, and occurs in a chronic form with remissions during which the patient may be comfortable and fairly active. The mortality fig-

ures range from 33.5 per cent by Hardy and Bulmer<sup>1</sup> in all cases over a period of twelve years, to 10 per cent by Barga and Buie<sup>2</sup> in a ten-year period at the Mayo Clinic. Spriggs<sup>3</sup> reports 20 per cent in nineteen years; Buzzard, Richardson and Turner<sup>4</sup> and Hern<sup>5</sup> give the figure as 28 per cent. Of those patients who survive and are not surgically treated, about 75 per cent are considered well enough during remissions to earn a living. Attacks often last for many months. Anything that contributes to cutting down the attacks obviously represents a substantial economic saving, as well as a reduction of suffering.

In 1930, Murray<sup>6</sup> first described psychogenic factors in ulcerative colitis. He was, at that time, connected with the Constitution Clinic at the Presbyterian Hospital, New York City, where various gastrointestinal conditions were being studied from various angles, including the psychologic, by Dr. George Draper's panels. Murray was struck by the well-marked time relation between the outbreak of an emotional disturbance and the onset of symptoms. He published the results of investigation of 12 cases, 4 of which were given in some detail. In another case, published later, he<sup>7</sup> gave a brief analysis of the psychologic factors involved. In this case, the patient's first memory (at the age of three) was of seeing her mother's coffin in the house. Murray followed out the effect of the attachment of the patient's libido, at this early age, to a dead imago. He emphasized the role of fear in the cases studied, and pointed out that diarrhea is a recognized infantile reaction to fear. He found marked emotional immaturity in these cases. Of 7 men, all were tied up with their mothers, except

\*From the Department of Psychiatry and the Department of Medicine, College of Physicians and Surgeons, Columbia University.

†Clinical professor of psychiatry, College of Physicians and Surgeons, Columbia University; assistant attending physician, Presbyterian Hospital.

1, who had found a mother substitute in an older sister. None of the men were married. Murray noted the most frequent conflict to be that between the attachment to the mother and the desire to get married. He emphasized the fact that it is not a sudden fright that causes the difficulty, but a new situation, which thereafter keeps the patient in a constant state of apprehension. Symptoms are an expression of resentment and hatred. The character traits can be recognized as those described as anal, with masochism evident, sadism concealed. This author expressed the opinion that the psychologic factors in ulcerative colitis are similar to those long recognized in simple diarrhea and mucous colitis.

Sullivan<sup>8</sup> recognized one of the patients in the Yale Hospital, New Haven, as one of those described in Murray's first paper. This patient had had a marked conflict over her forthcoming marriage. According to the history subsequently taken by Sullivan, she did marry a few weeks after leaving the Presbyterian Hospital, and immediately had had a return of diarrhea with blood. Murray had obtained significant facts from this patient relative to fear of childbirth, from which her mother had died. She was convinced that if she had a child, this would also be her fate. She was an ardent Catholic, and marriage had not been consummated during the first two years for fear that she would become pregnant. While she was in the New Haven hospital, her fear of pregnancy was gone into in an attempt to recondition her. She was given a gynecologic examination, and reassured. It was later learned that she had died two days after childbirth. Pregnancy had occurred immediately following her discharge from the hospital, and during it she had developed toxemia and a kidney disease. She had had no return of her colitis. As one comes to know ulcerative colitis cases, one believes that there was more than chance in the manner of this patient's death. Except for this one case, the Yale group reported excellent results with psychotherapy.

In 15 cases, Sullivan<sup>9</sup> found definite character traits. A sense of neatness was frequent, and most of the housewives were of the "fussy" variety. The outstanding characteristic was emotional tension. Ten patients of the series had prolonged tension, and it was this "stewing over things," as in Murray's cases, that was considered the important part of the condition. Eight of the 15 patients gave histories of financial worry, and in 6 cases, money matters played a prominent role in the total problem presented. Another very frequent factor was a close attachment to the mother or some other relative. In 2 wives and 1 husband diarrhea re-

lated to pregnancy and childbirth was demonstrable, in 2 others, it appeared chronologically, but the psychologic relation was not clear. Sullivan emphasized, as Murray did, the close relation between an actual precipitating event and the outbreak of diarrhea. In 11 of the 15 cases, the latter was within forty-eight hours of the former. In the remaining 4, the exacerbations of the disease were shown to be related to the nuclear conflict. Because of this coincidence, it was possible to concentrate on the emotional situation just prior to the attack.

Since the communications of Murray and Sullivan, increasing attention to the emotional factor in ulcerative colitis has been paid in the literature, emphasis is also beginning to be placed on the value of treatment of this factor. However, the only other systematic study of personality factors in ulcerative colitis recently reported is that undertaken by Wittkower,<sup>10</sup> who made a study of 40 unselected patients with ulcerative colitis in the Tavistock Clinic at St. Bartholomew's Hospital in London. Psychiatric disorders occurred far more frequently in these cases than in the average population. Such disorders were found to have antedated the colitis, and were so gross that a special control group was considered unnecessary. Carefully dated histories and verification with relatives showed that disturbing events preceded the onset, recurrence and increase of symptoms far enough to be more than a matter of chance. Twenty-eight of the 40 patients reported remissions of the disease. In 17, one or more relapses coincided with disturbances in their lives, usually with some external event. Many patients noticed a decline of their mental symptoms with the increase of their bodily ones. In 28 of the 40 cases, a clear-cut emotional trauma was considered serious enough to have been the precipitating factor of colitis. In 11, acute emotional stress, and in 17, prolonged emotional stress, ushered in the disease. The remaining 12 included those cases with the greatest psychologic deviation and those in which none was discovered. In 7, serious occupational, and in 4, severe financial difficulties preceded the onset. In 2 cases, colitis occurred under the strain of a forthcoming examination, in 6, there were domestic difficulties and in 2, dramatic love affairs were responsible. Sexual conflicts of an immature nature were important in 4. In 3 cases, colitis began in the course of pregnancy, and in 1, fear of labor was a major factor. Wittkower found no uniform personality make up, but his cases fell into three groups, with common characteristics within the group, a fourth group consisted of the miscellaneous personality types. The

first group was characterized by obsessional traits, the second, which was made up completely of women, by hysterical traits, and the third by depressive or schizoid trends. The personalities in childhood coincided with those in adult life, except that there was often an exaggeration of characteristics after maturity.

Sullivan<sup>9</sup> reports the most systematic attempt at treatment of ulcerative colitis along psychologic lines. The Yale group found by experience that patients could be helped more by procedures directed toward improvement of their personal problems than by therapy directed toward the colonic symptoms. This treatment was carried on on the medical wards by the general medical staff, and a psychiatrist was consulted only in the more difficult cases. Usually, the first month was spent in working up the laboratory data and establishing the general medical regimen. The patients were placed on a low-residue diet, with additional vitamins, and were given symptomatic therapy with bismuth, kaolin and belladonna. None of these procedures seemed to give more than symptomatic relief. The disease was either unchanged or aggravated until progress could be made along psychotherapeutic lines. Sullivan emphasizes the fact that weeks must be spent in getting the confidence of the patient, and that the problem would be very much more complicated if it were not for the amazingly close chronological association between an emotional episode and the onset of bloody diarrhea. He stresses the time necessary to get at even the conscious psychologic difficulties, and gives examples. He makes 60 per cent a conservative estimate of the incidence of ulcerative colitis on a psychogenic basis.

During the last ten years, I have seen 25 cases of ulcerative colitis at the Presbyterian Hospital. These have not been unselected cases, since most of them were referred by physicians for psychiatric consultation and treatment. A number of them have been followed for five to eight years, and a few have been studied intensively. Of 14 such cases, which comprised 2 men and 12 women, 8 showed a pathologic attachment to a relative; in 6, the death of this relative had been of paramount importance. Indecision about marriage was marked in 2 unmarried members of the group, and in 2 others, engagement and marriage were the precipitating causes of the first attack. In 2 cases, the first onset of symptoms was associated with childbirth, which also played a prominent role in another. Money difficulties had special significance in 4 cases. As a group, the patients were not well-adjusted sexually, although this did not generally stand out as the presenting problem.

The following cases illustrate typical findings in emotionally conditioned ulcerative colitis. Because Case 1 deals with one of the most frequently encountered therapeutic problems, — emotional emancipation from domineering relatives, — it is given in some detail. Two other cases of this series, which present a comparable family situation, have been reported elsewhere.<sup>11, 12</sup> In Case 2, the disease was precipitated by childbirth under conditions that kept alive a chronic conflict. In Case 3, the loss of a parent, with resulting depressive and suicidal trends, played the determining role.

### CASE REPORTS

CASE 1. F. A., a 26-year-old Italian housewife, was admitted to the Presbyterian Hospital in February, 1938, for bloody diarrhea. She first had intermittent attacks of diarrhea with mucus and blood associated with abdominal pain 6 years before entry, when she had been hospitalized for 7 weeks. This was followed by two more attacks within a year, both requiring hospitalization — one over a 2-month period. The patient was well for a year preceding the attack that brought her to the hospital, except for the occasional appearance of blood in the stools. A month later, when she reached the hospital, she was having twenty stools a day, with blood and mucus and a moderate amount of pain.

Physical examination was negative except that the abdomen was tender to palpation over the sigmoid and ascending colon. The liver had descended to the costal margin and was tender on palpation. The spleen was not palpated. The temperature was 102°F., the pulse 120, the respirations 20, and the blood pressure 120/80.

Examination of the blood showed a red-cell count of 4,350,000 with a hemoglobin of 79 per cent, and a white-cell count of 10,000. The stools contained mucus and gave a ++++ guaiac reaction; no ova or parasites were noted. *Escherichia coli*, *Streptococcus viridans* and *Clostridium welchii* were obtained on culture. A barium enema showed an irritable proximal colon; the descending colon appeared smooth and suggested ulcerative colitis. Proctoscopy revealed that the mucosa bled readily, was grayish brown and edematous, and was sprinkled with numerous small and moderate-sized ulcerations. The basal metabolism was -5 per cent.

The patient's attending physician in the hospital, suspecting that emotional factors were contributory in this case, referred the patient for psychiatric consultation and treatment, which were undertaken while she was still in the hospital. She was thoroughly co-operative, and volunteered the information that she herself had noticed a definite relation between emotional upsets and the attacks of diarrhea, which were usually preceded by a prodromal headache.

The patient was put on a low-residue diet and a course of pectin-agar, then of Anayodin, and then of sulfanilamide, supplemented with luminal, tincture of belladonna, paregoric and bismuth subcarbonate. She ran a fever of 103°F. intermittently, with a fairly persistent leukocytosis and elevated sedimentation rate. For 6 weeks, she passed from ten to twelve stools a day; after this, the number of stools gradually diminished until finally, by the 9th week, there was only one a day. There was no

definite correlation between clinical improvement and the medication administered

During the first psychiatric interview, the patient immediately began a discussion of the family, and this continued to be the main subject of the contact. She had been married at 17, and her husband at 21, against the wishes of both families, who, however, later accepted the marriage. She and her husband lived with his family, who did everything possible for them. Her husband was the pet of the family, the youngest of a number of unmarried siblings. His family immediately adopted the patient, and it became impossible for her and her husband to develop any real feeling of independence. Even when they went to live alone, his family supplemented their income and belongings, and were sensitive to any objections. They did not like her family, and because of this her mother visited her only once in 2 or 3 months, although she did not live far away, and she usually found some member of the husband's family there when she did come.

Two weeks before the attack that brought the patient to the hospital, one of her sisters in law had visited her and had made some gestures of reconciliation in connection with a quarrel that had developed during the Christmas holidays. The patient's husband was thoroughly in sympathy with her wish to become independent of his family, but there were so many of them that she had begun to believe that it was hopeless and that she might as well give in.

After several psychiatric interviews, an underlying depression came to the surface. The patient had periods of crying and expressed the opinion that her case seemed hopeless, although this had not been her attitude when she entered the hospital. It became quite clear, with further observation, that this hopelessness largely referred to the family situation. The patient told in some detail of the way in which her husband's family tyrannized her, especially after the outbreak of her first attack of colitis. They tried to prevent her going out at all on the basis of her health. She feared that, whenever she returned home from any excursion, one of her husband's family would be there to administer a rebuke. On one occasion, the mother-in-law informed a sister-in-law that the patient had gone to visit her mother. The sister-in-law promptly went to the patient's home, awaited her return and told her that she had just been talking to a physician, who said that it was not good for the patient to be out. When the patient intimated that she understood the ruse, the sister-in-law became very angry. The patient felt that before her illness it had been one thing to stand up for her rights, but since there was danger of recurrences of her colitis she did not dare to be so outspoken as formerly. The family was getting back the hold they desired. (One is reminded of the statement of another patient in this series,<sup>6</sup> whose mother would rather have her sick and at home than well and away.)

The history also showed that the couple had practiced coitus interruptus for the preceding 4 years, and because there was a history of anxiety and the possibility that some of the patient's symptomatology might be on the basis of an anxiety neurosis, she and her husband were advised about better sexual hygiene, and she was given an appointment at the Contraceptive Clinic.

The patient made a gradual recovery from this attack. After a few months in another locality, she and her husband moved back to the vicinity of his family because of school opportunities for their children, but this time they were on an entirely independent economic basis. The patient had begun to assert herself and had gained

courage to stand up for her rights—among others, the privilege of seeing her own family when she wished to without the criticism of his family. A year after hospitalization, she believed that the relation with her mother in law and sisters in law was improving. However, one brother in law still refused to speak to her, and another was very insulting and was outraged if any of her friends or family visited at the same time he did. When the patient explained to him that he had no right to act in this way toward guests in her own home he parried by reiterating how good he had been to her when she had been ill. She pointed out that this had nothing to do with the present problem, and he reluctantly accepted this point of view and was polite and friendly on succeeding visits. At this time, she seemed to be working gradually through her enslavement to her husband's family.

In the fall of 1939, she reported that she had been entirely free from symptoms for 3 months. She had had a slight recurrence, which could be laid to a return of the family difficulty. A great deal of her improvement was referred to the fact that a sister in law had returned with her baby to the parental home, and that the family had turned its attention and domination from the patient to this woman and her child. The patient was much relieved that her husband's family had some other object for their attention than herself. She was feeling and looking very well.

Three months later she reported a return of bleeding and she was convinced more than ever that this was related to the old family difficulty. She found that one of the sisters in law, although very nice to her face had been telling petty stories that tended to put the patient at odds with other members of the family. The patient then came to the conclusion that the only solution was to cut off entirely from her husband's family because attempts at reconciliation were successful only for a short time and she believed that the difficulties were incurable with which her husband concurred. She did not harbor resentment, but realized that the hold they had had on her when she was first married arose because of the affection that she had for them. This, she felt, had been destroyed by the things they had done and she did not anticipate that separation from them would any longer cause difficulty. It will take time to determine whether this situation is actually solved or only ameliorated.

CASE 2 S. M., a 48 year old, obese Jewish housewife, was admitted to the Presbyterian Hospital in February 1937, complaining of intermittent diarrhea of 11 years duration with two to six watery movements with mucus each day. The history stated that several attacks had been precipitated by emotional traumas, that diarrhea had first occurred 10 days after the birth of her first child and that blood had appeared in the stool following the birth of her second child.

On physical examination, the fundi showed sclerosis the thyroid gland was palpable but not enlarged and the abdomen was obese and pendulous, with slight tenderness in the left lower quadrant but no spasm. No masses or viscera were felt. The heart and lungs were normal. The temperature was 99.4°F, the pulse 96, the respirations 22 and the blood pressure 150/85.

Examination of the blood showed a red-cell count of 3,700,000 with a hemoglobin of 75 per cent and a white cell count of 8200. The nonprotein nitrogen of the blood serum was 36 mg per 100 cc. The stools gave a ++ guaiac reaction and showed no mucus. The urine was normal. The blood Wassermann reaction was negative. Proctoscopy showed lesions typical of ulcerative colitis. A

barium enema showed advanced ulcerative colitis. X-ray study revealed small areas of translucency in the tip of the gall bladder, indicating calculi, but with normal physiologic functions.

During the 10 weeks in the hospital, the case was considered interesting because of its chronicity without any demonstration of marked anemia or evidence of chronic disease on inspection. There was no relief from bismuth, diet or rest in bed. The patient was given a series of four autotransfusions, with radiation of the blood by ultraviolet light. These did not result in any improvement, and she was discharged to the Out-Patient Department, where she was followed.

Information obtained 6 months later showed that the patient had been unable to become pregnant during the first 14 years of marriage. A year and a half before her pregnancy, she had taken treatment for sterility, and at about the same time she acquired a lover, since her husband had proved sexually unsatisfactory to her. She was convinced that her first child had come from this union. She had been unable to believe that she was pregnant for some time, but when convinced of it she had been of two minds. One was joy at the idea of having a child, and the other was conflict and conscience over its paternity. This conflict came to a climax after the child's birth, and was increased by doubts whether it would live. The child did live, and is now perfectly healthy. Its coming had been a considerable source of interest to friends and neighbors on account of the patient's 14 years of barrenness. Her husband had likewise been pleased, and never suspected that the child was not his. The patient stated that she had never told anybody about the situation, not even her sister, but that *not a single day had passed without its being on her mind.*

The patient was certain that her husband was responsible for the second pregnancy, which occurred after 6 months. She was not clear why she had this child except that she took no precautions. She considered the interval between the pregnancies too short, and was resentful because she had had no rest from the first.

The patient did not improve dramatically following this revelation, but did seem considerably relieved in her mind. She continued to hold her own, was able to do her housework, and had brief periods of normal stools. Her lover died about a year after her discharge from the hospital. The environmental situation held little hope of improvement, and further psychotherapy did not seem to be the answer to the problem. The patient was referred to Dr. Thomas T. Mackie's service at the Roosevelt Hospital, New York City, and a report from that hospital stated that during the following year her course had been one of slight improvement, with minor periodic exacerbations. No infective agent was revealed.

CASE 3.\* L. B., an 11-year-old girl, was admitted to the Babies Hospital, New York City, in July, 1937, because of chorea and diarrhea. One sister was reported to have had intermittent attacks of diarrhea, with blood-streaked stools, for the previous 2 years. In March, the patient had begun to have intermittent attacks of loose stools, with some lower abdominal pain. About June 1, the mother had noticed rectal bleeding, with flecks of blood in the stools. A private physician had advised admission to another hospital, where x-ray studies of the colon were negative. During the 2nd day of her stay in this hospital, the patient had developed generalized choreiform movements. She had been removed from this hospital and

given three injections of triple typhoid vaccine at home. The chorea had progressed for the 10 days prior to admission to the Babies Hospital, and the child had become unmanageable at home.

Physical examination showed an asthenic, undernourished child who was thrashing about the bed with violent choreiform movements involving the entire body. On the skin about the angles of the mouth were patchy, vesicular, somewhat encrusted fissures, spreading inside the mouth and involving the buccal mucosa and the mucous membranes beneath the tongue, where there was an irregular, dirty, ulcerated lesion about 1 by 2 cm. The heart was not enlarged. A soft apical systolic murmur was present. The abdomen was scaphoid. The liver edge was palpable just at the costal margin. The spleen was not palpated. There were no gross neurologic changes. The temperature was 100.2°F., the pulse 120, the respirations 18, and the blood pressure 105/70.

The blood showed a red-cell count of 3,000,000 with a hemoglobin of 56 per cent, and a white-cell count of 18,150 with 77 per cent polymorphonuclears and 21 per cent lymphocytes. Subsequently, after gross hemorrhages, the red-cell count dropped to 1,500,000 with a hemoglobin of 28 per cent. The urine showed a faint trace of albumin, with much sediment and debris and granular casts. The stools were negative for pathogenic organisms. A smear of the mouth ulceration revealed no Vincent's organisms. Stool examinations frequently showed occult blood, but no ova or parasites.

On sedation with Chlorotone over a 2-week period, the choreiform movements entirely subsided, but the diarrhea continued unabated, with nine to eighteen stools a day. Proctoscopic examination showed granular rectal and sigmoid mucosa, with multiple points of bleeding but no large ulcerated areas. Because of rapidly developing anemia, the patient was given a series of citrated transfusions, with some rise in the red-cell count and hemoglobin. She was placed on a high-carbohydrate diet and given concentrated vitamin preparations, both by mouth and parenterally. Two weeks after admission, she became maniacal, thrashed about the bed and was uncontrollable. A neurologic consultant attributed the behavior to Chlorotone poisoning, and the drug was discontinued; the maniacal symptoms disappeared, and no further choreiform movements were noted. One month after admission, the patient had several large massive hemorrhages, amounting to between 300 and 500 cc. of bright-red blood from the rectum and followed by collapse. Rectal bleeding continued for 4 or 5 days, after which it subsided and the patient improved slightly, although her condition was considered too grave throughout this period to warrant ileostomy and cecostomy.

At about this time, a psychiatric consultation was first requested. The patient had been depressed and had talked of suicide; the history showed that her father had committed suicide the preceding fall, and that she had been very attached to him, and had continued to be disturbed by his loss. According to the history, the mother was a very difficult person, and the patient would not see any member of her family except her sisters. Her condition was too grave to permit any intensive psychotherapeutic procedures, and it was decided to follow her, in the hope that her physical condition might improve sufficiently to permit psychotherapy. Her condition, however, continued to grow worse. The patient was given a high-protein, high-calorie diet, with concentrated vitamin products, feeding being given by nasal tube because it was refused by mouth. She complained of abdominal

\*I am indebted to Dr. Rustin McIntosh for permission to include this case report.

pain, and an opiate was resorted to freely. She began to run a markedly elevated axillary temperature, between 102 and 103°F. The condition became graver, and diarrhea continued unabated, the stools being thin and slimy, and numbering between sixteen and twenty-five a day. The entire perianal area became red and erythematous. The patient gradually failed and expired on September 29. Permission for autopsy was obtained, and the typical picture of a chronic ulcerative colitis, with perforation of the colon at one place, was found. The heart showed fresh rheumatic lesions, but these were not considered extensive enough to have contributed to her death.

The final note in the child's chart stated that she had died on the first anniversary of her father's suicide; which was also her mother's birthday. Subsequent check of the father's death certificate showed that she had not died on the exact date, but within a week of this anniversary. It is of interest that this mistake, apparently obtained from some member of the family, should have crept in; and although it might have made the story more striking had she died on the anniversary, there is good reason to believe that the case actually represented one of indirect suicide.

### DISCUSSION

Except for basic factors relating emotions to disturbances of the large bowel, the psychophysiologic mechanism of ulcerative colitis is not yet understood. Sullivan<sup>9</sup> raised the question of whether stimulation of centers in the diencephalon, due to emotional stress, and the whipping up thereby of peristalsis in the small intestine may not lead to the emptying of abrasive digestive juices into the large bowel, or whether the enzymes may not be more potent or the mucosa less resistant in such cases. There is, in any event, a surface digestion of the mucosa that makes bacterial invasion easier, and ulceration results. Because of the patient's inability to solve his problems, hypermotility of the intestine persists, with constant irritation and chronic colitis.

Findings in mucous and spastic colitis may eventually help in elucidating the mechanism. White, Cobb and Jones<sup>13</sup> have recently published a monograph on this subject. The question whether ulcerative colitis represents a more advanced form of mucous or spastic colitis has been raised from time to time. Buzzard, Richardson and Turner<sup>4</sup> state that mucous colitis did not precede the development of ulcerative colitis in any of their 116 cases. Cullinan,<sup>14</sup> Spriggs<sup>3</sup> and others have had experience similar to that at the Presbyterian Hospital. However, certain personality factors and mechanisms do show a marked similarity, bearing out Murray's original conjecture. If spastic colitis and ulcerative colitis are in large measure the result of personality factors and conflicts, one would expect certain similarities since the organ affected is the same, although the deciding determinants

might be sufficiently different to make it rare for both disorders to appear in the same person.

The most interesting personality factors in relation to spastic colitis have been worked out by Alexander<sup>15, 16</sup> and his group at the Chicago Psychoanalytic Institute. Unfortunately, space does not allow a discussion of this interesting subject except to say that, in contrast to the gastric, peptic-ulcer type, he found that the cases of spastic colitis do not stand responsibility well, or if they do during good health, they indulge their dependence to a marked degree when ill. The Yale investigators<sup>17</sup> have made the same observation on cases of ulcerative colitis, and have dubbed this group the "giver-uppers." Alexander stressed the symbolic use of feces under some circumstances as a gift, in others as an expression of hostility, based on varying developmental regressions. In connection with the use of feces for hostile purposes, he calls attention to the use of offensive substances for defensive purposes, as in the skunk. Feces as the symbolic equivalent of a baby was clear in one case, a confusion that seems to have been present in one of my series.<sup>11</sup>

Much could be said of the relation of personality to disease of the colon. Alexander compares the gastric type with the phobic, and the colonic type with the compulsive neurotic. Both reactions occur in ulcerative colitis, the compulsive reaction being by far the more prominent. My impression is that the difference lies in the more narcissistic organization of the personalities in ulcerative colitis, with the underlying reaction more a psychotic than a psychoneurotic one. In some cases, the symptoms mask a severe depression. Perhaps the recurrent character of the disorder is significant in this regard. In several cases, the disease seemed definitely a type of organic suicide. This conclusion was also independently arrived at by the Yale group.<sup>17</sup> It is premature to make definite pronouncements on the character of the underlying neurosis, because this factor apparently differs. I believe, however, that in many cases there is a direct relation between the severity of the physical reaction and the underlying psychopathology. Psychoneuroses rarely cause death; psychoses frequently do.

### SUMMARY

A survey of the literature on the psychiatric aspects of ulcerative colitis shows that certain characteristics are commonly found in patients suffering from the disease. They are apt to have a fixation on some member of the family, usually the mother, and conflict develops in situations threatening this dependence, especially engagement and



barium enema showed advanced ulcerative colitis. X-ray study revealed small areas of translucency in the tip of the gall bladder, indicating calculi, but with normal physiologic functions.

During the 10 weeks in the hospital, the case was considered interesting because of its chronicity without any demonstration of marked anemia or evidence of chronic disease on inspection. There was no relief from bismuth, diet or rest in bed. The patient was given a series of four autotransfusions, with radiation of the blood by ultraviolet light. These did not result in any improvement, and she was discharged to the Out-Patient Department, where she was followed.

Information obtained 6 months later showed that the patient had been unable to become pregnant during the first 14 years of marriage. A year and a half before her pregnancy, she had taken treatment for sterility, and at about the same time she acquired a lover, since her husband had proved sexually unsatisfactory to her. She was convinced that her first child had come from this union. She had been unable to believe that she was pregnant for some time, but when convinced of it she had been of two minds. One was joy at the idea of having a child, and the other was conflict and conscience over its paternity. This conflict came to a climax after the child's birth, and was increased by doubts whether it would live. The child did live, and is now perfectly healthy. Its coming had been a considerable source of interest to friends and neighbors on account of the patient's 14 years of barrenness. Her husband had likewise been pleased, and never suspected that the child was not his. The patient stated that she had never told anybody about the situation, not even her sister, but that *not a single day had passed without its being on her mind.*

The patient was certain that her husband was responsible for the second pregnancy, which occurred after 6 months. She was not clear why she had this child except that she took no precautions. She considered the interval between the pregnancies too short, and was resentful because she had had no rest from the first.

The patient did not improve dramatically following this revelation, but did seem considerably relieved in her mind. She continued to hold her own, was able to do her housework, and had brief periods of normal stools. Her lover died about a year after her discharge from the hospital. The environmental situation held little hope of improvement, and further psychotherapy did not seem to be the answer to the problem. The patient was referred to Dr. Thomas T. Mackie's service at the Roosevelt Hospital, New York City, and a report from that hospital stated that during the following year her course had been one of slight improvement, with minor periodic exacerbations. No infective agent was revealed.

CASE 3.\* L. B., an 11-year-old girl, was admitted to the Babies Hospital, New York City, in July, 1937, because of chorea and diarrhea. One sister was reported to have had intermittent attacks of diarrhea, with blood-streaked stools, for the previous 2 years. In March, the patient had begun to have intermittent attacks of loose stools, with some lower abdominal pain. About June 1, the mother had noticed rectal bleeding, with flecks of blood in the stools. A private physician had advised admission to another hospital, where x-ray studies of the colon were negative. During the 2nd day of her stay in this hospital, the patient had developed generalized choreiform movements. She had been removed from this hospital and

given three injections of triple typhoid vaccine at home. The chorea had progressed for the 10 days prior to admission to the Babies Hospital, and the child had become unmanageable at home.

Physical examination showed an asthenic, undernourished child who was thrashing about the bed with violent choreiform movements involving the entire body. On the skin about the angles of the mouth were patchy, vesicular, somewhat encrusted fissures, spreading inside the mouth and involving the buccal mucosa and the mucous membranes beneath the tongue, where there was an irregular, dirty, ulcerated lesion about 1 by 2 cm. The heart was not enlarged. A soft apical systolic murmur was present. The abdomen was scaphoid. The liver edge was palpable just at the costal margin. The spleen was not palpated. There were no gross neurologic changes. The temperature was 100.2°F., the pulse 120, the respirations 18, and the blood pressure 105/70.

The blood showed a red-cell count of 3,000,000 with a hemoglobin of 56 per cent, and a white-cell count of 18,150 with 77 per cent polymorphonuclears and 21 per cent lymphocytes. Subsequently, after gross hemorrhages, the red-cell count dropped to 1,500,000 with a hemoglobin of 28 per cent. The urine showed a faint trace of albumin, with much sediment and debris and granular casts. The stools were negative for pathogenic organisms. A smear of the mouth ulceration revealed no Vincent's organisms. Stool examinations frequently showed occult blood, but no ova or parasites.

On sedation with Chlorotone over a 2-week period, the choreiform movements entirely subsided, but the diarrhea continued unabated, with nine to eighteen stools a day. Proctoscopic examination showed granular rectal and sigmoid mucosa, with multiple points of bleeding but no large ulcerated areas. Because of rapidly developing anemia, the patient was given a series of citrated transfusions, with some rise in the red-cell count and hemoglobin. She was placed on a high-carbohydrate diet and given concentrated vitamin preparations, both by mouth and parenterally. Two weeks after admission, she became maniacal, thrashed about the bed and was uncontrollable. A neurologic consultant attributed the behavior to Chlorotone poisoning, and the drug was discontinued; the maniacal symptoms disappeared, and no further choreiform movements were noted. One month after admission, the patient had several large massive hemorrhages, amounting to between 300 and 500 cc. of bright-red blood from the rectum and followed by collapse. Rectal bleeding continued for 4 or 5 days, after which it subsided and the patient improved slightly, although her condition was considered too grave throughout this period to warrant ileostomy and cecostomy.

At about this time, a psychiatric consultation was first requested. The patient had been depressed and had talked of suicide; the history showed that her father had committed suicide the preceding fall, and that she had been very attached to him, and had continued to be disturbed by his loss. According to the history, the mother was a very difficult person, and the patient would not see any member of her family except her sisters. Her condition was too grave to permit any intensive psychotherapeutic procedures, and it was decided to follow her, in the hope that her physical condition might improve sufficiently to permit psychotherapy. Her condition, however, continued to grow worse. The patient was given a high-protein, high-calorie diet, with concentrated vitamin products, feeding being given by nasal tube because it was refused by mouth. She complained of abdominal

\*I am indebted to Dr. Rustin McIntosh for permission to include this case report.

these patients will be symptom-free carriers and hence will constitute a serious public-health menace.

Laboratory experiments have demonstrated that some micro-organisms, among which is the gonococcus, develop a sulfonamide fastness that is retained by many subsequent generations and causes the organisms to lose none of their characteristics. It has also been shown that gonococci that have been made resistant to sulfanilamide are also resistant to sulfapyridine. It is not yet known whether these laboratory experiments have any clinical significance.

The mere fact that a patient with a gonococcal infection obtains a cure after having been treated with a sulfonamide does not justify accrediting the cure to chemotherapy. As a matter of fact, if given sufficient time during which the body defenses are permitted to function, most patients recover from gonorrhea regardless of the type of treatment. Therefore, time must be taken into account when one attempts to evaluate any plan of treatment. There is general agreement among those who have worked with the sulfonamides that if they are to be effective there will be evidences of clinical response within a very few days, and cases that do not show a response within five days will usually not be benefited by chemotherapy, no matter how long it is continued.

In an analysis of the reports of a large number of patients who had been treated in the Genitourinary Clinic of the Boston Dispensary in the presulfonamide days, it was found that no patient had been cured by local treatment within two weeks. It therefore seemed justifiable to credit cure to chemotherapy if the use of one of these compounds resulted in cure within two weeks. Approximately 1500 case histories of patients who have been treated with chemotherapy are available but, because eight different compounds have been used, no one group is yet large enough to warrant accepting the findings as conclusive. The appraisal studies excluded patients who had had their infection for more than one week before coming to the clinic or who had any previous treatment, and also those who did not remain under observation long enough for an adequate bacteriologic study after they became symptom free.

The results with sulfanilamide and sulfapyridine, which were reported in a previous communication,<sup>2</sup> were as follows. In the group treated with sulfanilamide, 48 per cent were classified as clinical failures, and 23 per cent more as bacteriologic failures—a cure rate of 29 per cent. And in the group treated with sulfapyridine, 5 per cent

were classified as clinical failures and 40 per cent more as bacteriologic failures—a cure rate of 55 per cent. All cases that remained clinically active for two weeks were classified as clinical failures, and those that became symptom free within two weeks and subsequently had one or more positive cultures were classified as bacteriologic failures. No serious reactions were noted in any patients treated with sulfanilamide or sulfapyridine. However, a large number of patients who were treated with sulfanilamide complained of dizziness and lassitude, and 40 per cent of those treated with sulfapyridine complained of gastrointestinal symptoms. These mild toxic reactions caused many patients to discontinue the drug against advice. In about half of each group, a drop of 30 to 50 per cent was noted in the white-cell count.

Four hundred and forty cases of gonococcal infection in men have been treated at the Boston Dispensary with sulfathiazole, but only 265 of these comply with our evaluation standards: that is, entrance to the clinic during the first week of infection with no previous treatment, and observation for a sufficient length of time to carry out a series of cultural studies. Of the 265 cases, 41 (15 per cent) were clinically active at the end of the second week, and in addition 26 (10 per cent) became asymptomatic within two weeks but had one or more positive cultures between the first and eighth weeks after becoming symptom free. The remaining 75 per cent represents the cure rate that can definitely be attributed to sulfathiazole.

There was no significant difference in the cure rates of those cases that had and those that did not have local treatment. Except for its alleged case-holding properties, there is no indication for local treatment in the cases that respond to sulfathiazole. Toxic symptoms were almost entirely absent, and none were serious enough to cause the patient to discontinue the drug. However, since drug fever, rash, headache, nausea and kidney complications have been reported by other investigators, it should not be concluded that sulfathiazole is entirely without toxic possibilities.

In this series, there were no blood changes other than an occasional insignificant drop in the white-cell count. The combined sulfathiazole in the blood stream varied from 0.5 to 6.0 mg. per 100 cc., and there was no correlation between the blood concentration and clinical response. Some of the failures showed the highest concentration.

Last year, the pooled case reports of patients treated with sulfanilamide from five clinics in different sections of the country were analyzed and reported by Pelouze et al.<sup>3</sup> That study showed a 30 per cent cure rate with sulfanilamide. The

same group is now studying the efficiency of sulfathiazole, and the results will be reported next June. From the available figures, it appears that the report will credit sulfathiazole with a cure rate of approximately 70 per cent and an asymptomatic carrier rate of from 5 to 6 per cent.

Another group<sup>4</sup> has, since December, 1940, been conducting a rapid appraisal of chemotherapy in gonorrhea in men. An average of 100 reports a week are being sent to a central tabulating unit for statistical analysis. Although this study has not been completed, 77 per cent of the patients treated with sulfathiazole are becoming symptom free within two weeks, compared with 40 per cent of those treated with sulfanilamide. Positive laboratory tests are being reported in only 3 per cent of the patients who have been symptom free for fourteen days.

These studies correspond with the experience at the Boston Dispensary—that is, they show the definite superiority of sulfathiazole to sulfanilamide in bringing about an early clinical response. The difference between the percentages of the bacteriologic failures in the three groups can be accounted for by the fact that most of the positive cultures in the Boston Dispensary group were obtained during the first two weeks after the patients became symptom free, whereas the positive cultures in the other two groups were obtained after the patients had been symptom free for two weeks.

The few cases that do not respond to chemotherapy still present a therapeutic problem. A small number of cases respond to a second course of sulfathiazole given ten to fourteen days after the first course, but no infection responds to a third course. Many patients who are not cured by sulfanilamide or sulfapyridine become symptom free soon after sulfathiazole treatment is started, but no patients in whom sulfathiazole fails respond to either sulfanilamide or sulfapyridine. Some form of local treatment is the best one can offer in cases in which the sulfonamides are unsuccessful. In men, potassium permanganate

irrigations, hand injections of one of the silver salts, and moderately skillful prostatic massage, when indicated, result in cure of most of these gonococcal infections.

A factor that makes the evaluation of any treatment of gonorrhea extremely difficult and is partly responsible for the variation in the figures reported by different clinics is the high lapse rate, which in some cases is 100 per cent. The lapses from treatment at the Boston Dispensary are about equally divided among cases that were clinically active and those that were inactive at the time of the last clinic visit. It is not known whether the patients in the former group lapsed because they became symptom free before the time of the next expected visit, or because they did not and consequently went elsewhere for treatment. If there were an opportunity of carrying out adequate bacteriologic studies in the patients who lapsed after they became asymptomatic, the figures would be more significant.

Present methods of treatment could be improved if more were known about the biology of the gonococcus, man's defense mechanism to gonococcal infection, and the mode of action of the sulfonamides. Because many outstanding scientists are devoting considerable time to these problems and are constantly adding information, sulfonamide failures may soon be extremely rare. Gonorrhea would then be a much less important disease than it has been throughout the ages, because destructive complications, the result of uncontrolled infections, would be almost nonexistent.

475 Commonwealth Avenue

#### REFERENCES

1. Pelouze, P. S. Gonorrhea and sulfanilamide: an effort toward clinical orientation. *Trans. Am. Neisserian Med. Soc.* 4:34-41, 1938.
2. Cox, O. F., McDermott, M., and Hinton, W. A. Chemotherapy and the early cure of gonococcal infection. *Trans. Am. Neisserian Med. Soc.* New York 6:49-52, 1940.
3. Pelouze, P. S., Barnes, R., Clark, A. L., Fox, O. F., Deakin, R., Onstott, R. H., Usilton, L. J., and Vonderlehr, R. A. Gonorrhea in the male: results of treatment with sulfanilamide. *J. A. M. A.* 115:1630-1633, 1940.
4. Cox, O. F., and Watkins, J. H. A cooperative plan for the rapid appraisal of the chemotherapy of gonorrhea in the male. *Am. J. Syph., Gonor. & Ven. Dis.* 24:732-736, 1940.

## RECENT ADVANCES WITH CHEMOTHERAPY IN THE TREATMENT OF INFECTIONS OF THE URINARY TRACT\*

EDWARD N COOK, MD†

ROCHESTER, MINNESOTA

**S**URVEYING the advances made in the field of chemotherapy in the past decade, those who are primarily interested in urology cannot but be proud of the contributions made by the workers in this specialty. In 1931, Clark<sup>1</sup> and Helmholz<sup>2</sup> first demonstrated a scientific approach to the treatment of infections of the urinary tract. It is true that their chemotherapeutic agent was synthesized in the body by a prescribed diet, but their work immediately prompted many others to attempt the sterilization of urine in the body by administering various chemicals orally or intravenously. Rosenheim<sup>3</sup> reported the results of his work with mandelic acid, and one of the first and finest chemotherapeutic agents came into wide use; this drug, it is true, has a limited use, and certain very definite conditions must be satisfied if it is to be effective. A few years later, the advent of the sulfonamide compounds was heralded with great acclaim, and this group of drugs has been of great aid in cases in which the administration of mandelic acid has not been satisfactory.

Because sulfanilamide is very reactive chemically, a multitude of derivatives have been synthesized, many of which have proved to be of even greater value than the parent substance in the treatment of certain types of disease.

A discussion of all these compounds is impossible. This paper therefore reviews briefly the experimental and clinical data on mandelic acid, sulfanilamide (*p*-aminobenzenesulfonamide), azo sulfamide (disodium 4 sulfamido phenyl-2-azo-7-acetyl amino-1-hydroxy naphthalene 3, 6-disulfonate), sulfapyridine (2-sulfanil aminopyridine) and sulfathiazole (2-sulfanilamidothiazole).

## MANDELIC ACID

Perhaps the most thorough experimental work in testing the efficacy of these various compounds against the organisms usually found in the urinary tract has been done by Helmholz. Soon after the publication of Rosenheim's report on mandelic acid, Helmholz<sup>4</sup> presented the results of his studies *in vitro*. To be effective, the drug must be present

in the urine in a concentration of at least 0.5 per cent, and the pH of the urine must not be greater than 5.5. By using varying concentrations of the drug in specimens of urine in which the pH varied, he was able to show that the usual gram negative bacilli are rather easily killed at the concentration of mandelic acid and at the pH mentioned previously. *Streptococcus faecalis* can also be destroyed when these conditions are satisfied, however, other streptococci, staphylococci and micrococci are not destroyed.

It is thus clear that a general grouping of the infecting organism is necessary before this drug is used as a chemotherapeutic agent. Cultures are not necessary, but helpful. Gram's stain suffices in most cases to demonstrate the presence of gram negative bacilli or *Strep. faecalis*. When the use of mandelic acid has been decided on, one essential condition must be satisfied, that is, renal function must be normal. At the Mayo Clinic, some untoward reactions have been observed when this drug was administered in cases in which the blood concentration of urea was higher than 40 to 50 mg per 100 cc.

The importance of an adequate dose and of the limitation of fluids during the use of mandelic acid is well known. If the urine cannot be sterilized in eight to ten days, it is advisable to discontinue the drug and administer it again after a rest period of one week. Provided the desired concentration can be obtained in the urine, and an adequate pH maintained, the urine should become sterile. If it does not, there undoubtedly is some complicating urologic lesion.

## SULFONAMIDES

I have been impressed with the progress that has been made with the sulfonamide group of compounds in the field of therapeutics. Their history, chemistry and pharmacology cannot be discussed here. There is no satisfactory explanation for the mode of action of these drugs. One cannot help believing that the drug has a direct action on the organism itself, or that it acts through an intermediary substance as yet not definitely known. Any effect produced through the immune processes of the body remains to be proved; at present, there are no experimental data that definitely reveal any real stimulation of phago-

\*Presented at a meeting of the New England Section of the American Urological Association, Boston, February 27, 1941.  
†From the Section on Urology, Mayo Clinic, Rochester, Minnesota.  
†His reactor in urology, Mayo Foundation.

easy to administer the equivalent of more than 100 gr. (6.6 gm.) of the drug daily to a patient by this method. Sulfapyridine and sulfathiazole may be given intravenously in the form of the sodium salts when desired, but this is rarely necessary. Occasionally, an 0.8 per cent solution of sulfanilamide for a continuous irrigation may be used in certain cases of severe cystitis, particularly when incrustations are present.

### Toxic Manifestations

There is no question that the sulfonamide compounds should never be given without close observation of the patient. These drugs should never be given unless the patient can be seen in twenty-four to forty-eight hours; many of the more serious reactions occasionally noticed may thus be averted. However, no serious difficulty is usually encountered in administering these drugs to urologic patients. This is undoubtedly because the dose we use is relatively much smaller than that generally used. I do not consider determinations of the concentration of these compounds in the blood necessary in the proper handling of patients suffering from infections of the urinary tract.

It is not necessary to describe in any detail the many signs and symptoms of toxicity that follow the administration of the sulfonamides. However, the value of close observation in cases of urinary infection should be re-emphasized. By such observation, many of these untoward reactions can be averted when they are incipient. Generally, one can say that azosulfamide is less toxic than sulfanilamide and its more closely related derivatives. Although sulfapyridine produces considerable nausea, sulfathiazole usually produces a mild nausea for the first day or two, but this disappears later. This drug is tolerated by a larger number of patients than any other sulfonamide compound. During its administration in the dose we have used, we have seen gross hematuria in only two or three cases, and microscopic hematuria infrequently. This is usually attended with the finding of sulfathiazole crystals in the urine. In no case, however, have we observed renal colic or anuria.

### SUMMARY

The sulfonamide compounds have contributed greatly to the treatment of infections of the urinary tract. It is essential to study the particular organism and the coexisting lesions present in each case. If therapy is not successful, the patient is entitled to a complete urologic investigation before further therapeutic measures are employed. The required dose in the treatment of infections

of the urinary tract is much lower than that needed in the general field. Untoward reactions are not usual because of the reduced dose; however, close observation is necessary to avert these reactions.

### REFERENCES

1. Clark, A. L. Escherichia coli bacilluria under ketogenic treatment. *Proc. Staff Meet., Mayo Clin.* 6:605-608, 1931.
2. Helmholz, H. F. The ketogenic diet in the treatment of pyuria of children with anomalies of the urinary tract. *Proc. Staff Meet., Mayo Clin.* 6:609-613, 1931.
3. Rosenheim, M. L. Mandelic acid in the treatment of urinary infections. *Lancet* 1:1032-1037, 1935.
4. Helmholz, H. F. Mandelic acid in the treatment of urinary infections. *Am. J. Dis. Child.* 52:1037-1039, 1936.
5. Mellon, R. R. Clinical and experimental aspects of mode of action of sulfanilamide-sulfapyridine compounds. *Ohio State M. J.* 36:1263-1274, 1940.
6. Mellon, R. R., and McKinney, R. A. The biologic nature of sulfapyridine's bacteriostatic effect against the pneumococcus. *Proc. Soc. Exper. Biol. & Med.* 42:677-679, 1939.
7. Braasch, W. F., and Cook, E. N. Recent advances in the treatment of infections involving the urinary tract. *Tr. Am. Urol. A. (South-eastern Branch)* 1:29-37, 1934.
8. Helmholz, H. F. The use of sulfathiazole as a urinary antiseptic. *J. Urol.* 45:135-145, 1941.
9. Sickler, James R. A study of the bactericidal activity of sulfanilamide in the urine at various levels of hydrogen ion concentration. *J. Urol.* 43:906-916, 1940.

### DISCUSSION OF DR. COX'S AND DR. COOK'S PAPERS

DR. CHAMP LYONS (Boston): Dr. Cook's paper has emphasized one or two things that were summarized by Dr. Cox. The perfect urinary antiseptic has not been found. Mandelic acid, under certain circumstances, has very definite advantages. It should not be completely abandoned, and yet there are cases of urinary infection in which one does not wish to concentrate the urine to the point that is necessary for the successful use of mandelic acid therapy, or in which the kidney is unable to establish a pH consistent with the most efficient working of the drug. Under such circumstances, one resorts to the various other compounds. It is interesting that sulfathiazole seems to be the most widely effective drug, and that it is not necessary to use it in concentrations recommended for the treatment of pneumonia. Adherence to that principle will undoubtedly save grief, but sulfathiazole given for five to nine days or longer carries with it a real risk of setting up some of the toxic side reactions that are so undesirable. Even on the dosage recommended for the treatment of gonorrhea, I have seen granulocytosis.

I still think that a frequent white-cell count is imperative, since one must look out particularly for signs of toxic hepatitis. In dealing with surgical patients who have open wounds and who are receiving sulfathiazole, one should routinely determine the prothrombin level of the blood on about the fourth or fifth day, because bleeding of such wounds is associated with fairly early evidence of toxic hepatitis.

In patients with restricted biliary output, the administration of small amounts of sulfathiazole increases the biliary output, again a hepatotoxic manifestation.

The work of Lilly and others, recently published in the *United States Public Health Reports*, has emphasized the significance of diet in relation to the development of toxic symptoms. Rats fed on a low-protein diet deficient in methionine and cysteine showed a much greater incidence of toxic manifestation. Many of the patients coming under urologic care have by force been restricted in their dietary intake. The way is paved for the development of toxic symptoms.

The one point that I wish to emphasize is that, regardless of the dose, the period from the fifth to the ninth day

of therapy is beset with difficulties in the way of development of toxic symptoms.

In surgical cases an effort is made to conduct operative intervention in association with chemotherapy within the relatively safe period,—before the fifth day,—so that if chemotherapy must be discontinued because of the onset of toxic symptoms the surgical part of the procedure and the time of possible flare up of the recent infection will have elapsed.

DR CHESTER S. KEEFER (Boston) My interest in urinary tract infections began some years ago with the study of colon bacillus bacteremias, and since that time a large number of chemotherapeutic agents have been introduced except for a few changes the general principles of the treatment of urinary tract infections have remained essentially unaltered.

No case has been completely studied, in my opinion unless the specific infective agent has been isolated and until the underlying anatomic lesion that is responsible for this infection has been recognized.

The first of these two principles can usually be carried out without much difficulty, provided a good bacteriologic study is made. One cannot distinguish sufficiently between the various gram negative and gram positive organisms by the simple gram stain.

The second point is that the anatomic lesions that underlie urinary tract infections can usually be recognized by careful and expert study. The most serious lesion that predisposes to urinary tract infection is, of course, some type of obstruction. I hesitate to mention that to a group such as this since it is a commonplace but unless obstructive lesions are relieved many disappointing results occur in the use of chemotherapeutic agents.

Besides the relief of obstructions, other factors enter into the prognosis in urinary tract infections: the age of the patient, the presence or absence of bacteremia, the type of infecting organism and the type of complication as mentioned by Dr Cook.

Colon bacillus infections usually are particularly stubborn in patients with diabetes. Furthermore, patients who have thrombophlebitis of small intrarenal veins do not respond to chemotherapeutic agents. In most cases such patients respond only to nephrectomy and one may suspect such a condition if there are chills and fever with bacteremia but without pus, or if an operation on the genitourinary tract has been performed.

There may also be a very poor outlook in cases of ureteral obstruction that cannot be relieved by the usual simple operative procedures. One must accordingly take these facts into consideration in planning treatment.

During the past year at the Massachusetts Memorial Hospitals sulfathiazole has been used almost exclusively because *in vitro* experiments, as well as studies of patients, have shown that this drug is more effective than sulfanilamide in the treatment of many infectious agents in addition the concentration of urine that is effective may not need to be so high as that with sulfanilamide. The question of the optimal concentration in the urine has, of course, excited considerable interest.

Dr Cook reported the work of Halmholz who discovered that a level of 30 mg per 100 cc caused marked inhibition. Of course one can produce effective inhibition with 30 mg per 100 cc in the urine provided that the inoculum is small; this is a significant point in interpreting any *in vitro* experiment. On the other hand with a very large inoculum and a great deal of concentration it is often very difficult to show any stasis of growth.

Dr Lyons properly emphasized a significant fact in the giving of the sulfonamide drugs—the reaction of the urine need not be taken into account. Some of the conflicting

opinions concerning the variation in the activity of these drugs with the reaction are due to the fact that the inoculum, the number of organisms and the amount of drug used in the experiments have not been properly assessed.

The concentration in the urine is of the utmost importance. A relatively high concentration can be obtained with relatively small doses by mouth. If 15 gm of sulfathiazole is given in a 24 hour period and if the urinary output is limited to 1500 cc there will usually be a concentration of about 100 mg per 100 cc, this is generally sufficient to take care of the average case of urinary tract infection provided that the infection is not too heavy.

Finally I should again like to stress the fact that one does not need to pay attention to the reaction of the urine in most of these cases and that if one is unable to demonstrate a positive effect one should attempt to relieve obstructive lesions.

DR GEORGE G. SMITH (Boston) I was much interested when Dr Cook said about the use of mandelic acid in staphylococcus infections. I realize that his statements are based on *in vitro* experiments. The trouble with mandelic acid *in vitro* seems to be that one cannot reach the pH of the urine below 7.0.

A complication of sulfathiazole therapy that I happened to observe, although it may not be particularly new, might be worth mentioning. A sixty year old woman who was being treated by a surgeon for a septic sinus from an old encephalitis received 4 gm of sulfathiazole daily for five days. The fluid intake was not regulated. The patient was probably given very little fluid. At the end of five days she developed complete anuria and the nonprotein nitrogen rose very rapidly. At the surgeon's request I cystoscoped her. The bladder was normal and contained no urine. Sticking out of the left ureter was a small white speckle. The right ureter looked normal but, when I attempted to insert a catheter into it, proved to be obstructed. I prodded it with the catheter, and a great deal of muddy material was discharged after which I was able to get the catheter to the kidney. On the left side the catheter went more easily. I left these catheters in overnight and 90 ounces of urine drained. The patient made a rapid recovery so far as the kidney condition was concerned. In this case the sulfathiazole had crystallized in the urine and had obstructed the ureter. Dr Deming has reported similar cases with sulfapyridine.

DR RICHARD CHUTE (Boston) I should like to hear of experiences with the use of an 0.8 per cent solution of sulfanilamide as an irrigant. Possibly, Dr Quinby has some information. I know of several patients with postcatheterization cystitis—not my own—who have been treated and cured by local washes of sulfanilamide solution without any oral therapy, and I wonder if anyone has had similar experiences that would enrich the general knowledge.

DR WILLIAM C. QUINBY (Boston) The work to which Dr Chute refers concerns the use of a solution of sulfanilamide to irrigate the renal pelvis in cases in which for one reason or another, reactions to the solution by mouth occurred. In a few cases very definite relief was obtained by irrigation of the renal pelvis with such a solution and definite absorption can be demonstrated by examination of the blood after such an irrigation. I do not believe that we have had more than a case or two in the last year. Most of the patients were diabetic and therefore poorly resistant to infection or for some reason or other,—because of an alarming blood picture or because of fever,—it was considered unsafe to continue irrigation of sulfanilamide.

## TRAUMATIC OBSTRUCTION OF A MAIN BRONCHUS\*

## Report of a Case

M. DAWSON TYSON, M.D.,† AND JOHN S. LYLE, M.D.‡

HANOVER, NEW HAMPSHIRE

**A**N injury of the chest wall, with crushing or actual section of the main bronchus, is a rare occurrence and is nearly always fatal. We have found in the literature case histories of 8 patients who survived such an injury, with resultant complete bronchial obstruction.<sup>1-6</sup> In these cases, the force producing the injury was regularly of a very severe degree, such as that caused by a truck or car passing over the thorax or by a heavy weight falling upon the chest. In some, there were numerous rib fractures; in others, there was no evidence of bone injury. The ages varied from three years to thirty-three years at the time of the accident. All the patients were in extremely critical condition immediately after the injury. In all but 1 case, convalescence was prolonged.<sup>2</sup> After recovery, 6 of the 8 patients returned to normal life. One other, reported by Krinitzki,<sup>1</sup> had remittent pain on the affected side, and seven years later developed tuberculosis of the uninjured lung. The remaining patient, reported by Supino,<sup>5</sup> had severe dyspnea and continual pain on the injured side; death occurred in ten years, and was apparently a direct result of the injury.

The left main bronchus was injured in 5 cases, and the right main bronchus received the damage in the other 3. Three patients came to autopsy between ten and twenty years after injury, and 2 underwent exploratory thoracotomies twenty and thirty years later (Rienhoff<sup>3</sup>). In these 5 cases, it was observed that the lung was shrunk to the size of a fist, was of leathery consistence, and occupied the upper posterior portion of the corresponding hemithorax. It was Rienhoff's opinion that in his 2 operative cases, the pulmonary arteries, as well as the bronchus, were occluded. In the autopsied cases, section of the atelectatic lung revealed that the bronchial tree was filled with a jellylike mucus, and the whole organ presented the picture of "drowned lung," familiar to thoracic surgeons. In Krinitzki's<sup>1</sup> case, the patient died of a tuberculous infection of the remaining lung, which started seven years after the injury. It is noteworthy that no tuberculous involvement of the atelectatic lung was found.

Compensatory changes take place in almost the same manner as in patients who have sustained a

total pneumonectomy, namely by increase in the size of the remaining lung, shift of the mediastinum toward the involved side, elevation of the diaphragm and contracture of the hemithorax on the side of the injury. It is interesting to note that chest pain and dyspnea have been described in several cases during the period of intrathoracic readjustment; this aspect is discussed later. Infection of the injured lung has apparently not taken place.

Treatment has varied in the different cases, but the chief methods employed consist in supportive measures at the time of injury, with oxygen administration for relief of dyspnea and cyanosis. Aspiration of air from the pleural cavity was performed in some cases. Jones and Vinson<sup>4</sup> report incision above the sternal notch for relief of mediastinal emphysema. Rienhoff's patients complained of pain in the chest on the injured side twenty and thirty years after the injury; exploratory thoracotomy, with release of pleuropericardial adhesions, gave relief in both cases. Four months after injury, Clerf<sup>6</sup> instituted pneumothorax on the injured side in 1 case and obtained relief of dyspnea on exertion.

The following case exhibited findings that led to a diagnosis of traumatic rupture of the left main bronchus, with complete occlusion.

## CASE REPORT

A 26-year-old man, with a chief complaint of weight loss, pain in the chest and dyspnea, was admitted to the Mary Hitchcock Memorial Hospital on December 4, 1938. He had been injured in an automobile accident during the preceding August and had been taken to a nearby hospital in a critical condition. A letter from his physician stated that at the time of the injury the patient coughed up bright-red blood. He was unconscious and cyanotic on arrival at the neighborhood hospital. Shortly after admission there, the temperature rose to 104.8°F., and the pulse reached 160. Supportive measures were employed, although their exact nature was not revealed. Improvement was very slow, and the patient left the hospital against advice on September 4, 1938, with a fracture of the left scapula, according to the statement of his physician.

At the Mary Hitchcock Memorial Hospital, it was found that the excursion of the left thorax was diminished. There were dullness to percussion and absent breath sounds over the left chest in the upper anterior and posterior aspects. The cardiac impulse was in the fourth interspace 16.5 cm. to the left of the midsternal line, and the trachea could be felt to the left of the midline. The vital capacity was 54 per cent of normal. Overexposed x-ray films showed that the whole trachea was deviated

\*From the Mary Hitchcock Memorial Hospital, Hanover, New Hampshire.

†Staff surgeon, Mary Hitchcock Memorial Hospital.

‡Assistant in thoracic surgery, Mary Hitchcock Memorial Hospital.

markedly to the left (Fig. 1). The left lung apparently occupied the upper portion of the left hemithorax, and the heart was displaced into the left chest. The diaphragm was elevated, and the intercostal spaces were narrowed. The right lung extended into the left chest,

compensatory changes had had time to take place. He was readmitted on January 31, 1939, feeling better and having gained 12 pounds. He still had dyspnea, however, and some pain in the left chest. The vital capacity was 47 per cent. The cardiac impulse was in the third interspace



FIGURE 1.

occupying about one third of this cavity. Bronchography demonstrated a complete obstruction of the left main bronchus 3 cm. distal to the tracheal bifurcation (Fig. 2). Bronchoscopic examination by Dr. John A. Murtagh demonstrated that the left main bronchus terminated blindly, and biopsy showed that the blind end was lined by normal bronchial mucosa.

The patient was allowed to go home for a month, to see what improvement would occur when further com-

in the axillary line. It was thought that the continued pain and dyspnea might be due to the sudden and marked shift of the mediastinal structures to the left; therefore, a pneumothorax was given in the left pleural cavity in an attempt to correct the mediastinal displacement. The initial inspiratory pressure was -38 cm. of water. Several pneumothorax fillings gave considerable relief of the dyspnea and pain, but this treatment was abandoned because of the development of fluid.



On March 7, the patient was again admitted to the hospital, complaining of a return of dyspnea and chest pain. X-ray examination showed a complete absorption of the intrapleural air and fluid. A series of pneumothorax injections was again performed. The initial inspiratory and expiratory pressures were  $-58$  and  $-44$  cm. of water, re-

In addition to the rarity of the condition, this case presents several points of interest. In the first place, the relief of pain and dyspnea by the use of pneumothorax suggests that the pull of the atelectatic lung was the cause of the symp-

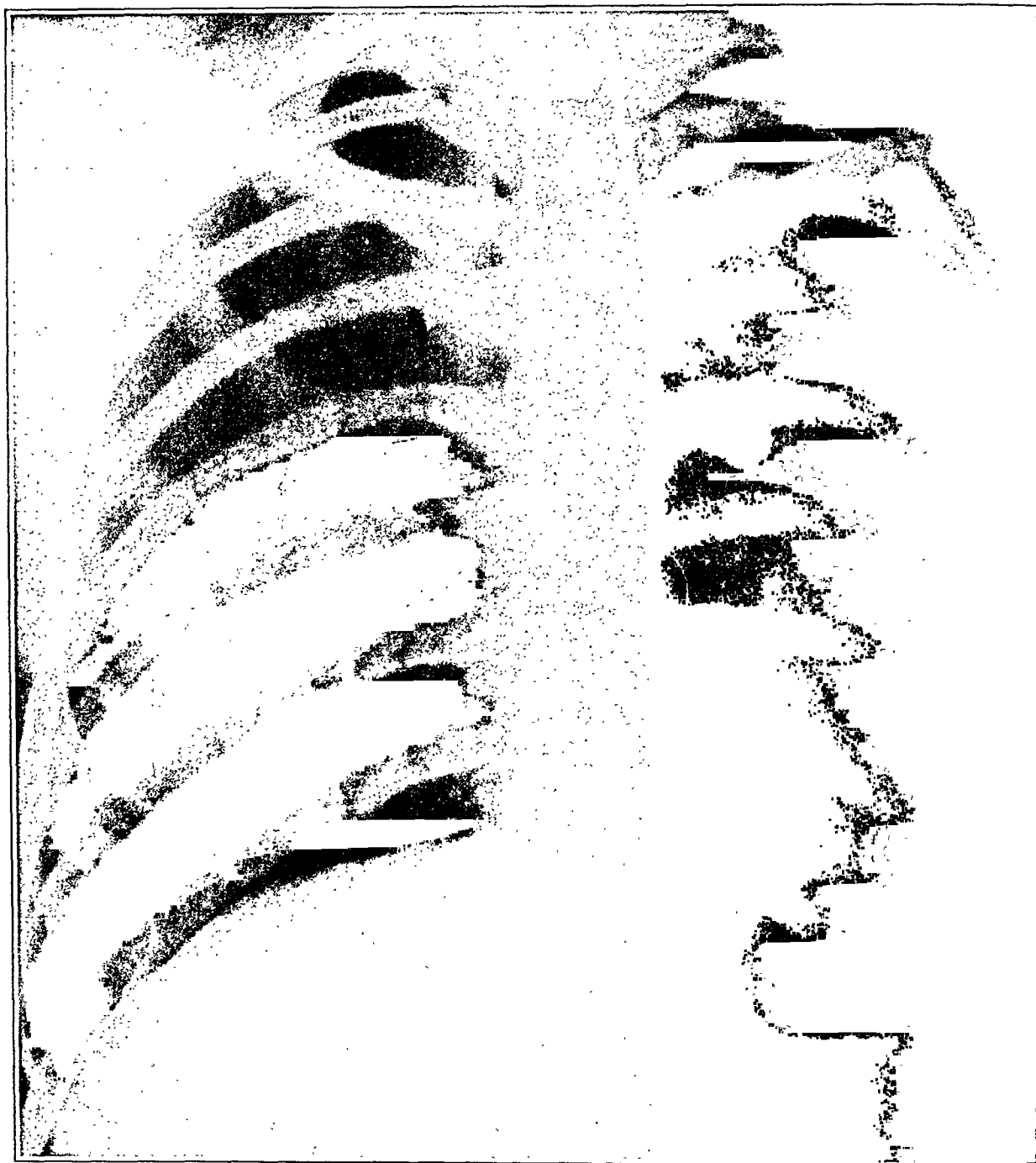


FIGURE 2.

spectively, at the time of the first injection. After several fillings, there was marked relief of chest pain and dyspnea, and the patient finally felt well enough so that the injections were discontinued. After a short stay at home, he was able to return to work and has remained well to date.

He was seen in the Out-Patient Department in February, 1940, when a pneumothorax needle was inserted into each pleural cavity; the pressure readings were  $-6$  and  $-8$  cm. respectively.

The high degree of negative pressure ( $-58$  and  $-44$  cm. on one occasion) certainly indicates that the pull may have been very strong. It is probable that this pull is a large factor in producing the contralateral pulmonary enlargement, although the compensatory changes in this case apparently did not take place rapidly enough to

prevent the formation of excessive negative pressures. It seems likely that the absorption of air from the pleural cavity after total pneumonectomy and the consequent negative pressure may be important factors in producing the compensatory changes in the remaining lung.

The absence of infection in the atelectatic lung is noteworthy in this case as well as in those previously reported. Although the condition of the lung seemed to favor a suppurative process, the fact that the bronchial obstruction was complete probably prevented contamination of the "drowned lung." As supportive evidence of this concept, Lemon<sup>7</sup> found in laboratory animals that a partial bronchial obstruction favored pulmonary infection, whereas infection was not encountered when the obstruction was complete.

The eventual development of emphysema in the remaining lung, because of overstrain of the elastic tissue, is a possibility. Bigger<sup>8</sup> points out that estimation of the intrapleural pressure on the sound side will give an index of the state of pulmonary elasticity. In the case reported, readings were taken on both sides fifteen months after the injury, and the pressures were found to be -6 and -8 cm., which could be considered to be in-

dicative of a normal elastic tone, although the eventual elasticity cannot be foretold. As stated by Bigger, circulatory embarrassment, if present, can be corrected at any time by thoracoplasty, but emphysematous changes are irreversible. It therefore seems logical to resort to thoracoplasty if successive pressure determinations show a dangerous decrease in pulmonary elasticity on the unaffected side.

### SUMMARY

A case of traumatic obstruction of a main bronchus is reported. Cases previously reported in the literature are briefly discussed, and certain physiologic aspects of the condition are considered.

### REFERENCES

- 1 Krutitzki, S. I. Zur Kasuistik einer vollständigen Zerreissung des rechten Luftröhrenastes. *Virchows Arch f path anat* 266 815 819 1928
- 2 Nicod, J. J., and Ureth, E. Rupture guérie d'une bronche principale. *Ann d anat path* 13 485-494, 1936
- 3 Rienhoff, W. F., Jr. Intra-thoracic anastomotic readjustments following complete ablation of one lung. *J Thoracic Surg* 6 254 277 1937
- 4 Jones, F. W., and Vinson, P. P. Nonfatal rupture of the left main bronchus from external trauma. *Surgery* 5 228 231, 1939
- 5 Supino, L. Antica frattura del grosso bronco destro con stenosi cicatriziale occlusiva. *Arch ital di anat e istol* 6 563 579, 1935
- 6 Clerf, L. H. Rupture of the main bronchus from external injury. *Surgery* 7 276-279 1940
- 7 Lemon, W. S. Personal communication
- 8 Bigger, I. A. Discussion of Rienhoff, W. F., Jr. Readjustments in thoracic cage and its contents following total and partial pneumonectomy. *South M J* 29 445 456 1936

## THE PROTEIN OF THE CEREBROSPINAL FLUID IN PATIENTS WITH CHRONIC ALCOHOLISM\*

ELLSWORTH H. TROWBRIDGE, JR., M.D.,† AND LAZARUS SECUNDA, M.D.‡

BOSTON

COMPARATIVELY few reports have appeared in the literature concerning the elevation of the protein of the cerebrospinal fluid in patients with chronic alcoholism. Because of the significance that is universally attached to the cerebrospinal-fluid protein in evaluating the neurologic status of a patient, more facts on this subject in alcoholic patients are needed. This study was undertaken primarily to establish the incidence of abnormal changes in the protein level in cases of chronic alcoholism of varying duration and severity.

The cerebrospinal fluid was examined in 641 cases of chronic alcoholism admitted to the Boston Psychopathic Hospital between 1929 and 1939. The ages of the patients ranged between sixteen and seventy years, with an average of forty-two years. They were classified as follows: delirium tremens,

129 cases; Korsakow's psychosis, 24 cases; alcoholic auditory hallucinosis, 145 cases; other types of alcoholic psychosis, 163 cases; and chronic alcoholism without psychosis, 180 cases. Six hundred and ten patients (95 per cent) had consumed an average of one pint of whiskey a day for five to thirty years. The remainder had drunk heavily for two to six months prior to entry.

One hundred and fifty-eight nonalcoholic patients with no evidence of organic disease of the nervous system were selected as control cases. The clinical diagnoses in these were as follows: dementia praecox, 83 cases; manic-depressive psychosis, 45 cases; involutional psychosis, 21 cases; psychosis due to metabolic disease, 6 cases; and psychoneurosis, 3 cases. The ages of these patients ranged between eleven and sixty years, with an average of thirty-six years.

The neurologic examination was performed within eighteen hours, and lumbar puncture with-

\*From the Department of Psychiatry, Harvard Medical School

†Senior physician, Boston Psychopathic Hospital; assistant in psychiatry Harvard Medical School

in six days of admission. The total protein of the cerebrospinal fluid was determined by the method of Dennis and Ayer.<sup>1</sup> All fluids with a protein

paresthesia of the feet, muscle weakness or atrophy and impairment of sensation. Of the 641 patients with chronic alcoholism, 108 (17 per cent)

TABLE 1. *Elevated Total Protein in the Cerebrospinal Fluids of Patients with Chronic Alcoholism and of Control Patients.*

DIAGNOSIS	No. OF CASES	CASES WITH ELEVATED TOTAL PROTEIN				TOTAL
		46-55 MG	56-75 MG	OVER 75 MG		
Chronic alcoholism with psychosis	461	47	35	14		96 (21%)
Delirium tremens	129	9	10	2	21 (17%)	
Korsakow's psychosis	24	2	1	2	5 (20%)	
Auditory hallucinosis	145	21	8	4	33 (23%)	
Other types of psychosis	163	15	16	6	37 (23%)	
Chronic alcoholism without psychosis	180	17	11	4		32 (18%)
Other psychoses (control patients)	158	10	5	0		15 (9%)

greater than 45 mg. per 100 cc. were considered abnormal. The Wassermann reaction of the spinal fluid was negative in all cases. The patients who had signs and symptoms consistent with a known organic disease of the central nervous system not due to alcohol were eliminated from this series. In the 641 cases reviewed, 461 had psychosis and 180 no psychosis.

The protein of the cerebrospinal fluid was elevated (greater than 45 mg. per 100 cc.) in 128 cases (20 per cent) of the total series, whereas in 158 control subjects only 15 (9 per cent) had an abnormal protein content (Table 1). There was little difference in the prevalence of abnormal protein of the cerebrospinal fluid in patients with and those without psychosis, the former group revealing 96 (21 per cent) and the latter 32 cases (18 per cent). The type of psychosis seemed to make little difference. Rosen<sup>2</sup> found in cases of chronic alcoholism with psychosis an abnormal protein in 52 per cent, in contrast with the 21 per cent of our series; Rosenbaum<sup>3</sup> found abnormal protein in 3 per cent of his cases of delirium tremens, in contrast with the 17 per cent of our series.

No correlation exists between the duration and the severity of the alcoholic psychosis on the one hand, and the protein content of the cerebrospinal fluid on the other (Table 2). Furthermore, the number of previous attacks of alcoholic psychosis has little influence on the protein of the cerebrospinal fluid. The patients with a history of one previous attack had protein values between 46 and 88 mg. per 100 cc., and 3 patients who had had 4, 6 and 13 attacks of alcoholic psychosis, respectively, had normal protein.

It might be suggested that the amount of the protein in the cerebrospinal fluid is essentially conditioned by the presence of polyneuritis. We therefore paid attention to the presence of polyneuritis in our cases. The criteria of neuritis were: hypoactive to absent knee or ankle jerks, tenderness or cramps of the calf, hyperesthesia and

had polyneuritis. In only 17 per cent of the cases of polyneuritis was there abnormal protein, where-

TABLE 2. *Relation of the Elevated Total Protein Content of the Cerebrospinal Fluid to the Duration of Disease in Patients with Alcoholic Psychoses.*

DELIRIUM TREMENS		KORSAKOW'S PSYCHOSIS		AUDITORY HALLUCINOSIS		OTHER TYPES OF ALCOHOLIC PSYCHOSIS	
TOTAL PROTEIN	DURATION OF PSYCHOSIS	TOTAL PROTEIN	DURATION OF PSYCHOSIS	TOTAL PROTEIN	DURATION OF PSYCHOSIS	TOTAL PROTEIN	DURATION OF PSYCHOSIS
mg / 100 cc.		mg / 100 cc.		mg / 100 cc.		mg / 100 cc.	
47	1 day	52	1 mo	46	15 days	47	4 days
47	4 days	55	6 mo	46	12 days	47	2 mo
50	4 days	63	2 mo	47	7 days	47	2 mo
50	3 days	87	2 mo	47	4 days	48	5 days
50	1 day	250	18 days	47	4 days	48	5 mo
52	3 days			48	17 days	49	5 days
52	2 days			48	10 days	49	1 mo
54	3 days			49	83 days	49	2 yr
55	6 days			50	18 days	49	6 yr.
57	3 days			51	17 days	50	5 days
57	5 days			51	56 days	50	5 days
61	1 day			52	14 days	51	3 mo
64	3 days			53	2 days	52	1 wk
66	3 days			53	15 days	53	5 days
66	4 days			55	6 days	55	3 mo
66	2 days			55	7 days	56	2 wk
67	4 days			55	15 days	56	2 wk
70	4 days			55	16 days	59	2 days
72	6 days			55	16 days	59	2 wk
87	2 days			55	36 days	60	5 days
95	9 days			55	4 days	61	4 days
				57	34 days	61	2 wk
				61	20 days	62	5 days
				61	2 yr.	62	5 days
				62	38 days	63	3 wk
				63	1 yr.	67	5 mo
				64	10 days	68	4 wk.
				68	14 days	68	6 mo.
				72	16 days	69	5 yr
				80	11 days	72	1 wk.
				82	8 days	74	3 wk
				88	16 days	77	2 mo.
				93	29 days	78	4 wk
						80	5 days
						80	2 wk
						96	4 mo
						100	1 yr.

as in 21 per cent of the cases of alcoholism without polyneuritis there was an abnormal protein.

#### SUMMARY

Of 641 patients with chronic alcoholism, 20 per cent had a protein of the cerebrospinal fluid greater than 45 mg. per 100 cc.

Abnormal protein of the cerebrospinal fluid was more than twice as frequent in patients with chronic alcoholism as in a series of control patients.

The presence, the duration and the number of previous attacks of an alcoholic psychosis had no influence on the protein of the cerebrospinal fluid.

The presence of polyneuritis has no significance in the production of the abnormal protein of the

cerebrospinal fluid, for a larger percentage of the alcoholic patients without polyneuritis had abnormal protein than patients with polyneuritis.

#### REFERENCES

1. Dennis, W., and Ayer, J. B. A method for the quantitative determination of protein in cerebrospinal fluid. *Arch. Int. Med.* 26:436-442, 1920.
2. Rosen, S. R. The cerebrospinal fluid total protein in the alcoholic psychopathies. *Am. J. Med. Sci.* 201:270-277, 1941.
3. Rosenbaum, M. The cerebrospinal fluid in delirium tremens. *J. A. M. A.* 116:2467, 1941.

## MEDICAL PROGRESS

### RENAL-FUNCTION TESTS\*

JOHN H. TALBOTT, M.D.†

BOSTON

#### COMMONLY USED TESTS OF RENAL FUNCTION

SEVERAL tests of renal function are commonly employed in the clinical consideration of kidney disorders. These include the testing of ability to concentrate solids, the measuring of excretion of phenolsulfonphthalein, pyelography after intravenous injection of Diodrast or other iodine compounds, and the determination of nonprotein nitrogen in the serum. Each of the tests is based on one or more recognized duties of the kidneys, which may show evidence of deterioration as a result of functional or morphologic change.

#### Ability to Concentrate Solids

The ability to concentrate solids maximally connotes normal tubular epithelium and is the first function to deteriorate in many renal disorders.<sup>1</sup> The ability to concentrate may be determined following reduction of fluid intake or following the injection of pituitary extract. If a subject with normal kidneys restricts fluids for twelve hours, urine specimens voided subsequently at hourly intervals show a specific gravity of 1.020 or greater. Following abstinence from fluid for thirty-six hours, 1.027 should be reached. The injection of pituitary extract<sup>2</sup> has the advantage that it requires little preparation of the patient. At a convenient time, 0.5 cc. of pituitary extract is administered subcutaneously. Urine samples are collected every half hour for three or more hours. A normal response is a specific gravity of 1.020

or greater. In extensive kidney disease, inability to concentrate above 1.014 is evident by either concentration test. In diabetes insipidus, the kidneys have a normal concentrating ability following the use of pituitary extract, but are unable to concentrate following restriction of fluids overnight.

#### Excretion of Phenolsulfonphthalein

The phenolsulfonphthalein test is a measure of the capacity of the tubular cells to excrete this substance. The procedure gives the most information if the amount of dye excreted is partitioned at frequent intervals rather than collected in one sample two hours after injection.<sup>3, 4</sup> During the first fifteen minutes after intravenous injection of 1.0 cc. of dye, a normal person should be able to excrete at least 25 per cent of the total amount. In advanced renal disease, less than 5 per cent may be excreted during this period.

#### Pyelography

Intravenous pyelography gives qualitative rather than quantitative information regarding renal function; nevertheless, the examination is useful to the internist as well as to the urologist. The various iodine preparations used for pyelography are handled by different renal processes, and if this procedure is interpreted as a renal-function test, it is essential to know which compound is used. Diodrast and Hippuran are excreted largely by tubular activity, whereas Skioidan is excreted largely by glomerular activity. Theoretically, it should be feasible to take advantage of the different paths of excretion, to distinguish between glomerular and tubular damage during the incipient stage of a renal disorder. At later stages, this is usu-

Reprints of articles in this series are not available for distribution, but the articles will be published in book form. The current volume is *Medical Progress: Annual, 1940* (Springfield, Illinois: Charles C. Thomas Company, 1941. \$4.00).

\*From the Medical Clinic, Massachusetts General Hospital, and the Fatigue Laboratory, Harvard University. These laboratories are supported, in part, by a grant from the Corn Industries Research Foundation.

†Associate in medicine, Harvard Medical School, and assistant physician, Massachusetts General Hospital.

ally not possible, since kidneys that cannot concentrate solids to a specific gravity above 1.014 during a concentration test are unable to concentrate iodine compounds sufficiently to be visualized by x-ray examination. Exceptions, however, do occur, and in this clinic, more than a dozen patients have been observed whose kidneys were unable to concentrate solids above 1.014 by carefully controlled clinical tests but were readily visualized by intravenous pyelography. Most of the patients who showed this unorthodox finding were suffering from a renal condition other than Bright's disease. In cases in which it was studied, the urine passed immediately after pyelography had a specific gravity above 1.020. The ability to concentrate, therefore, applied only to substances occurring naturally in the urine and not to foreign substances, such as iodine compounds. Diodrast is relatively nontoxic, and no untoward effects need be anticipated by its use in patients with advanced renal impairment.

#### *Serum Nonprotein Nitrogen*

The concentration of nonprotein nitrogen in the serum should not exceed 35 mg. per 100 cc. in healthy persons. Values greater than this usually indicate gross renal failure. An increase in concentration may appear temporarily in a variety of conditions, either from transient impairment of renal function or from an increased formation of nitrogenous waste products. Knowledge of the concentration of nonprotein nitrogen in the serum has been of inestimable service in clinical medicine, but values should be interpreted only after consideration of related findings and data and after determination of other tests of renal function.

#### PRECISE TESTS OF RENAL FUNCTION

All the tests mentioned above can be performed easily in the clinic, and all yield useful information. They are neither quantitatively precise nor sufficiently accurate, however, to detect small variations from the normal or to detect the early changes of anatomic renal disease. For example, it is quite possible for each of the tests to yield "normal results," yet more precise tests show a deficiency as great as 30 per cent in the amount of blood passing through the kidney or in the amount of glomerular filtrate formed. To obtain information regarding these functions, one must use the procedures that are known as clearance tests.

A little more than ten years ago, the concept of "clearance" was introduced in clinical investigation by Van Slyke and his associates<sup>5</sup>; since then, these tests have served an extremely useful function. Urea clearance and creatinine clearance, which were stud-

ied first, have in recent years been superseded by inulin and Diodrast clearance tests. Urea appears in glomerular filtrate, but a variable amount, depending on diuresis, is reabsorbed by tubular activity. Likewise, creatinine appears in glomerular filtrate, and an additional amount is excreted by the tubular cells. Since the clearance of both substances is an index of combined glomerular and tubular activity, it is understood why they are less attractive than the clearance tests devised and described by Smith,<sup>6-8</sup> which measure specific functions separately. The terms inulin clearance ( $C_I$ ), Diodrast clearance ( $C_D$ ), maximum tubular excretory capacity for Diodrast ( $T_{MD}$ ) and maximum tubular reabsorptive capacity for glucose ( $T_{MG}$ ) are gradually appearing in the medical literature, and before many years have elapsed they may be as readily understood as terms now in use in electrocardiography or in clinical chemistry.

The clearance procedures described by Smith are complicated. Nevertheless, it is hoped that modifications of them for clinical use may be made available before long. The tests as described are performed while the patient is fasting and lying

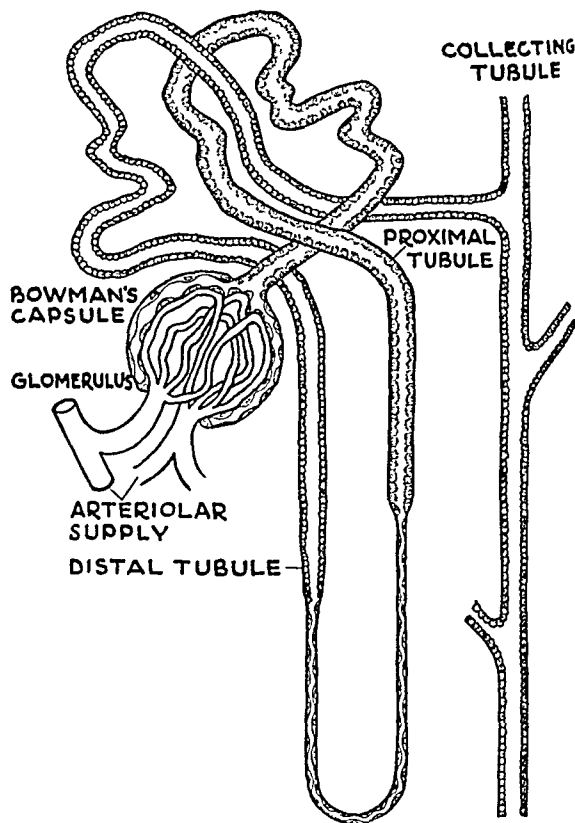


FIGURE 1. *Essential Features of a Typical Nephron in the Human Kidney.*

in the supine position.<sup>8</sup> A continuous intravenous injection is maintained throughout the test. A soft rubber catheter is retained in the bladder, and

urine is delivered without interruption into a container. It may be desirable to catheterize the ureters for 'split function' in certain subjects. This has been done on several occasions by members of the Urological Service at the Massachusetts General Hospital, and no serious obstacles have been encountered. Nor have any serious side or direct effects been noted as a consequence of the test, whatever technic has been employed. During the last four years, our laboratory has performed several hundred clearance tests, and it can be considered no more formidable a procedure than lumbar puncture or proctoscopy. The four tests may be performed during approximately three hours.

An explanation of the functioning unit of the kidney, the nephron, serves as an introduction to a detailed discussion of the clearance tests. A nephron is shown diagrammatically in Figure 1. This has been modified from Smith.<sup>6</sup> Included are glomerulus, convoluted and collecting tubules and a blood supply. It is assumed that blood from the afferent arteriole enters the glomerulus, continues into the efferent arteriole on leaving the glomerular capillaries and, after the functions of excretion and reabsorption are performed in the capillary network about the convoluted tubules, loses its identity as arterial blood and becomes venous. Approximately two million nephrons comprise the functioning renal tissue of an adult.

#### Inulin Clearance

Inulin clearance ( $C_i$ ) is used synonymously with "rate of formation of glomerular filtrate"<sup>6</sup>. Inulin is a starchlike polymer and, if chemically pure, is an ideal substance for use in determining the rate of formation of glomerular filtrate. Approximately 25 gm is necessary for a single test. Inulin is not metabolized by the body and is excreted by the kidneys if injected intravenously. The path of excretion is exclusively through the glomerular membrane, the tubules neither reabsorb nor excrete the substance. As an example, if the concentration of inulin is 100 mg per 100 cc. of plasma and if 125 mg of inulin is excreted by the kidneys into the bladder per minute, 125 cc of plasma must have participated in the formation of glomerular filtrate to allow this quantity of inulin to be excreted (Fig 2). The amount of inulin cleared by the kidneys and the amount of glomerular filtrate formed per minute are identical. These values are expressed as cubic centimeters of plasma cleared per minute. An average value is 125 cc per minute, and the normal range is between 100 and 150 cc per minute. Values should be corrected to a standard body surface area, and Smith has selected 1.73 square meters as the standard in his studies.

#### Diodrast Clearance

Diodrast clearance ( $C_d$ ) is assumed to measure "effective renal blood flow,"<sup>7</sup> that is, effective so far as formation of urine is concerned. An additional small amount of blood supplies inert structures in the kidney, such as connective tissue, and is not measured by Diodrast clearance. The Diodrast used in the determination is the identical iodine compound employed in intravenous

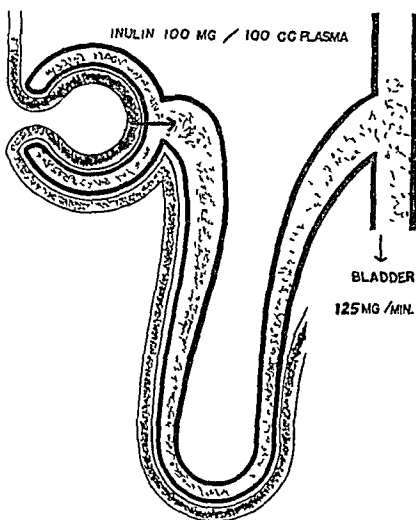


FIGURE 2 Inulin Clearance

Since the plasma contains 100 mg of inulin per 100 cc and since 125 mg of inulin per minute is excreted in the urine the glomerular filtration is 125 cc of plasma per minute.

pyelography. At low blood concentrations, approximately 10 mg per 100 cc of plasma, all the Diodrast entering the arterioles contiguous to functioning nephrons, is removed before the blood leaves the kidney. A portion is removed by the glomeruli, and the remainder is excreted by the tubules. It makes little difference for the calculation of renal blood flow how the nephron removes the Diodrast; the significant point is that the removal is complete in the venous blood returning from the kidneys. Diodrast, like inulin, is not destroyed by the body, and approximately all the Diodrast in the blood eventually finds its way into the urinary bladder. If the concentration of Diodrast in the plasma is 10 mg per 100 cc and if 7 mg of Diodrast is excreted per minute into the bladder, 700 cc of plasma must

have passed through the kidneys to allow for excretion of this amount of Diodrast (Fig. 3). Renal plasma flow, or  $C_D$ , therefore, is 700 cc. per minute. If whole blood contains 40 per cent cells

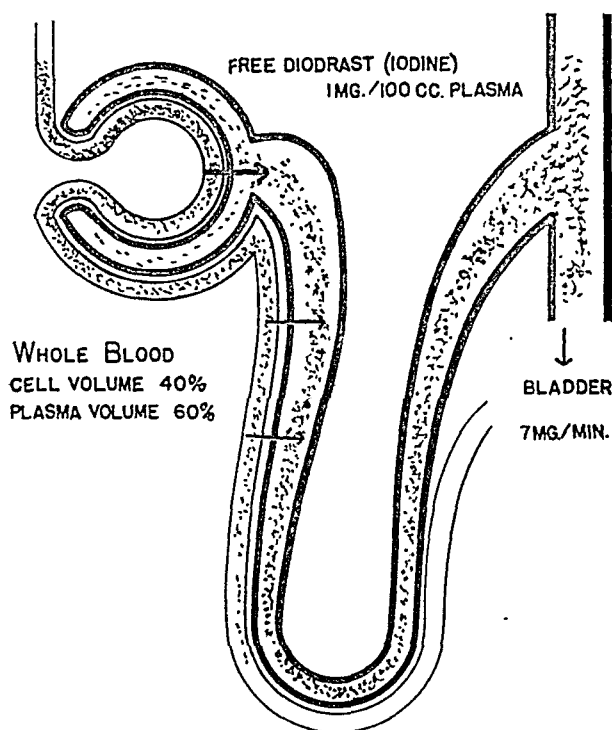


FIGURE 3. Diodrast Clearance (Low Plasma Concentration).

Since the plasma contains 1 mg. of Diodrast per 100 cc. and since 7 mg. of Diodrast per minute is excreted in the urine, the renal plasma flow is 700 cc. per minute; and since the plasma constitutes 60 per cent of the blood, the renal whole-blood flow is  $700 \div 0.60 = 1170$  cc. per minute.

and 60 per cent plasma, the effective renal flow of whole blood would be approximately 1200 cc. per minute, which is nearly one third the cardiac output. The average normal renal flow of whole blood is 1200 cc. per minute, the values ranging from 1000 to 1400 cc.

#### Tubular Excretion of Diodrast

$T_{MD}$  is the designation for the maximal capacity of the tubules to excrete Diodrast when a greater quantity is presented to them than they are able to handle.<sup>9</sup> This may be determined if the concentration of Diodrast in the plasma is elevated to 25 mg. per 100 cc. At such levels, not all the Diodrast is extracted from the blood as it is at low plasma levels, and a portion of the Diodrast appears in each of three fluids. The first portion appears in glomerular filtrate at the same concentration as it exists in the plasma. The second portion is excreted into the tubules by the tubular cells. The urinary excretion of Diodrast is com-

posed of these portions. If the total urinary excretion and the amount presumably excreted by glomerular filtration are known, the difference is the amount excreted by tubular epithelium. This constitutes the value,  $T_{MD}$ . The third portion is that left in the blood after the tubular cells have functioned maximally. This portion is disregarded and is not used in the calculation. For example, if the concentration of Diodrast in the plasma is 25 mg. per 100 cc. and the rate of formation of glomerular filtrate is 125 cc. per minute, 30 mg. of Diodrast per minute is excreted through the glomeruli (Fig. 4). If a total of 80 mg. per minute is excreted into the bladder, the difference between the total

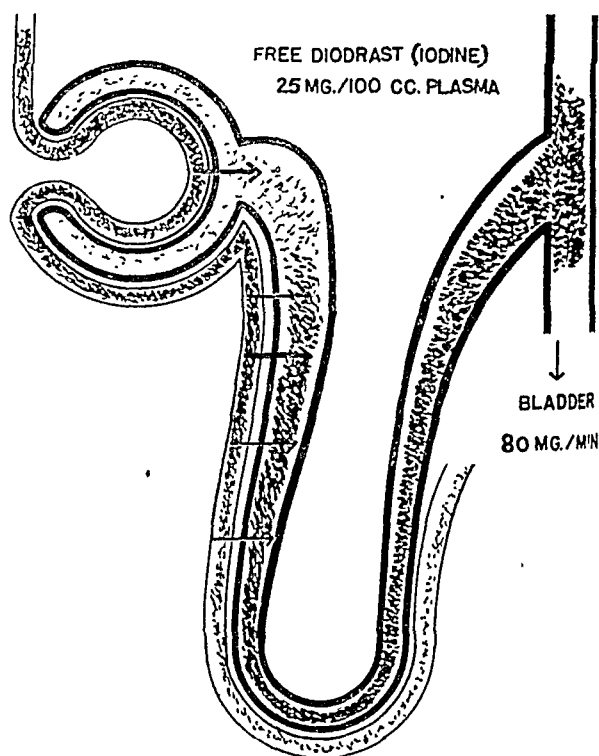


FIGURE 4. Diodrast Clearance (High Plasma Concentration).

Since the plasma contains 25 mg. of Diodrast per 100 cc. and since it is assumed that 125 cc. of plasma per minute passes through the glomeruli, the Diodrast excreted by the glomeruli is about 30 mg. per minute; however, since 80 mg. of Diodrast per minute is excreted in the urine, the maximal amount of Diodrast excreted by the tubules is  $80 - 30 = 50$  mg. per minute.

urinary excretion (80 mg.) and the amount present in glomerular filtrate (30 mg.) gives a value of 50 mg. for  $T_{MD}$ , a normal figure.

#### Tubular Reabsorption of Glucose

$T_{MG}$  is an index of the maximal capacity of the tubules to reabsorb a specific substance, glucose, when an excessive amount is presented to them.<sup>9, 10</sup> Thus, while  $T_{MD}$  measures the max-

imum capacity of the tubules to excrete a specific substance, *Tmc* measures their capacity to reabsorb a specific substance. For example, if the concentration of glucose in the plasma is elevated to

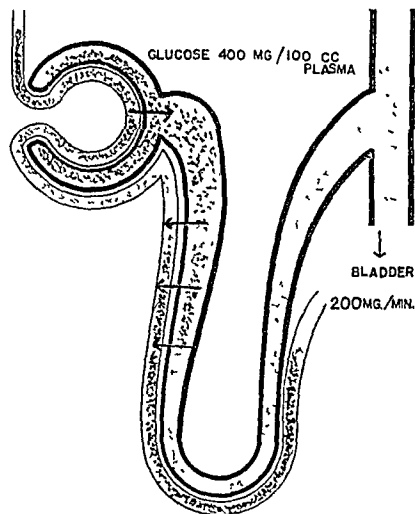


FIGURE 5 Glucose Clearance (High Plasma Concentration).

Since the plasma contains 400 mg. of glucose per 100 cc. and since it is assumed that 125 cc. of plasma per minute passes through the glomeruli, the glucose excreted by the glomeruli is 500 mg. per minute, however, since 200 mg. of glucose per minute is excreted in the urine, the maximal amount reabsorbed by the tubules is  $500 - 200 = 300$  mg. per minute.

400 mg. per 100 cc. and the rate of formation of glomerular filtrate is 125 cc. per minute, 500 mg. of glucose will appear in glomerular filtrate per minute (Fig 5). If only 200 mg. per minute appears in the urinary bladder, the difference between the glomerular excretion (500 mg.) and the total excretion (200 mg.) gives a value of 300 mg. for *Tmc*, the maximum amount reabsorbed from the

filtrate by the tubular cells; this is an average figure.

### SUMMARY

Several tests for renal function have been described. The procedures that are convenient to perform in the clinic include the testing of ability to concentrate solids, the measuring of excretion of phenolsulfonphthalein, pyelography after intravenous injection of Diodrast, and the determination of nonprotein nitrogen in the serum.

More exact information regarding the specific functions of the kidney may be derived from the various clearance tests. Inulin clearance and Diodrast clearance at low plasma levels measure rates of glomerular filtration and effective renal blood flow, respectively. Other substances might be employed to measure these functions, and would yield similar values. On the other hand, maximal tubular activity, as measured by the excretion of Diodrast or the reabsorption of glucose, is presumably specific, and with each new substance a different set of values would result. This qualification, however, does not detract from the significance of these determinations. In a subsequent progress report, the use of these methods in recognizing and differentiating various unusual renal disorders will be discussed.

### REFERENCES

1. Herr, R. C. Factors affecting the tests of kidney function. *Physiol. Rev.* 24:529-572, 1941.
2. Sodeman, W. A. and Engelhardt, H. T. Renal concentration test employing use of pituitary extracts: response of normal subjects. *Proc. Soc. Exper. Biol. & Med.* 46:688-691, 1941.
3. Chapman, E. M. and Halstead, J. A. The fractional phenolsulfonphthalein test in Bright's disease. *Am. J. Med. Sc.* 186:223-232, 1933.
4. Chapman, E. M. Further experience with the fractional phenolsulfonphthalein test. *New Eng. J. Med.* 214:16-18, 1936.
5. Moller, E., McIntosh, J. F. and Van Slyke, D. D. Studies of urea excretion. II. Relationship between urine volume and the rate of urea excretion on by normal adults. *J. Clin. Investigation* 6:427-455, 1928.
6. Smith, H. W. *The Physiology of the Kidney*. 310 pp. New York: Oxford University Press, 1937.
7. Oxford Physiology of the renal circulation. In *The Harvey Lectures Series* 35, 313 pp. Lancaster, Pa.: Science Press Printing Co., 1939.
8. Goldring, W., Chasis, H. Ranges, H. A. and Smith, H. W. Relations of effective renal blood flow and glomerular filtration to tubular excretory mass in normal men. *J. Clin. Investigation* 19:739-750, 1940.
9. Smith, H. W., Goldring, W. and Chasis, H. The measurement of the tubular excretory mass: effective blood flow and filtration rate in the normal human kidney. *J. Clin. Investigation* 17:263-278, 1938.
10. Shannon, J. A., Fisher, S. and Trout, L. The measurement of glomerular filtration in the normal dog. *Am. J. Physiol.* 133:752-761, 1941.



## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTE-MORTEM AND POST-MORTEM RECORDS AS USED  
IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

### CASE 28051

#### PRESENTATION OF CASE

A twenty-three-year-old freight solicitor was admitted to the hospital because of recurrent attacks of abdominal pain.

In the year preceding admission, he experienced three attacks of approximately similar character. In the last episode, which began a week before entry, the patient noted vague epigastric pain during an afternoon. He then ate a large dinner, and two hours later had severe, cramplike pains in the midabdomen and vomited; the pain subsided gradually, with bed rest and local application of heat. He took no food for the next forty-eight hours because of persistent nausea and vomiting. The bowels remained normal. At this time, he consulted a physician, who because of the presence of an abdominal mass in the right lower quadrant and localized tenderness, advised immediate hospitalization. The temperature and white-cell count were normal. The patient refused to enter the hospital and spent the next few days in an active week end in New York City. During this period, there was no pain or discomfort. When he returned to Boston four days later, he agreed to enter the hospital.

Except for the episodes described, the patient had been well. Two and a half years previously, the left foot was crushed in an automobile accident, requiring amputation below the knee, subsequent revisions of the stump and two nerve-crushing operations. Except for slight paresthesias, he had had no trouble with the stump for the year preceding entry.

On admission, the patient was well developed, with a well-healed amputation stump terminating 15 cm. below the left knee. Examination showed a tender, sausage-shaped mass in the right lower quadrant, beneath McBurney's point. The mass measured about 5 by 2 cm., and could be freely moved medially, during which procedure the pain was referred to the umbilicus. The rest of the examination was negative.

The temperature, pulse, respirations and blood pressure were all normal.

Examination of the blood showed a red-cell count of 4,990,000 with 14.7 gm. hemoglobin, and a white-cell count of 6500 with 62 per cent poly-

morphonuclears. The blood Hinton reaction was negative. The urine was normal.

A barium enema passed readily to the cecum, and entered the terminal ileum. There was a sharply defined, smooth concave pressure defect on the medial aspect of the tip of the cecum at the site of the appendix. This defect was constant, and could not be obliterated. It was not possible to fill the appendix. There was no evidence of mucosal ulceration.

On the second hospital day, an operation was performed.

#### DIFFERENTIAL DIAGNOSIS

DR. LELAND S. MCKITTRICK: May we see the x-ray films?

DR. JAMES R. LINGLEY: The lesion is seen best in the spot film (Fig. 1). Here is the ileocecal valve, and here the tip of the cecum, so that the

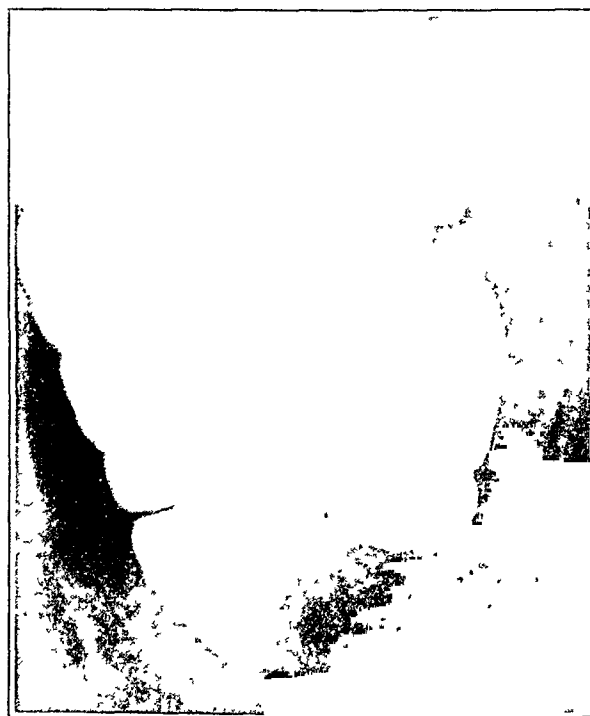


FIGURE 1. Spot Film of Cecum.

mass is in the appendix region. The mass appears to be outside the cecum, and there is no involvement of the mucosa. It does not look like a primary tumor of the cecum, and the deformity is due to pressure rather than to intrinsic involvement.

DR. MCKITTRICK: This patient had three episodes of pain over a period of a year, the last attack occurring a week before admission, when a mass appeared or was found when he was examined, forty-eight hours after the onset of the pain. No elevation in temperature or white-cell

count was associated with this mass. The pain was epigastric or midabdominal.

The history is a little bit difficult to interpret, and possibly we ought not to pay too much attention to it. Obviously, the patient was well enough, at the end of forty-eight hours with a mass in the right lower quadrant, to go to New York and not spend his time sitting around a hotel room. When he returned, he had more soreness—something definite—and therefore entered the hospital. We must assume that these attacks of pain were of short duration. There is little evidence of true inflammatory reaction associated with them, and there was no interference with bowel activity. We have a positive finding of a palpable mass in the right lower quadrant in a situation consistent with the location of the cecum. That mass was moderately tender. It was freely movable medially. It was felt a week following onset of symptoms. The temperature and white-cell count were normal, and there was no anemia. Apparently, whatever this mass was or whatever caused it, it had no effect on his general state, and therefore it is reasonable to assume it was not a progressive thing that had been going on over a period of a year.

We know that the patient had a tumor, and I cannot determine with any accuracy its nature. The x-ray evidence strongly suggests that it was not a tumor arising in the mucosa of the bowel. If it was a tumor of the cecal wall, it must have arisen from the outer layers of the bowel wall. Thus, it seems to me that certain things can reasonably be excluded. We have no evidence to justify a diagnosis of carcinoma of the cecum. His age does not exclude it, but he had had symptoms for a year, he probably had had little or no blood in the stools, since he had a normal red-cell count and hemoglobin, and there was no evidence of any ulceration of the mucosa by x-ray. I should be content to rule out a carcinoma of the cecum. Lymphoma, I presume, cannot so easily be excluded, because ulceration might not have been present. I do not know how to make that diagnosis with complete assurance, any more than I can exclude it. I am influenced by Dr. Lingley, who considers this to be pressure from without rather than an intrinsic process in the bowel itself. Someone might say that this was a mass of lymphomatous nodes giving pressure on the cecum, and that is a possible answer. If we talk about tumor arising in the bowel and not associated with or developing from the mucosa, we are limited to a lipoma. This could be present for a year without affecting the patient. It could cause recurrent episodes of pain and could be palpated perfectly well through the abdominal wall in a man who

was not very heavy. The recurrent attacks of pain would be due to attacks of intussusception, and these should be associated with periods of obstruction. But the bowels moved normally during attacks.

Among other conditions that are essentially of an inflammatory nature, tuberculosis can give a palpable tumor in this location. This is one of the commoner sites of the hyperplastic type of tuberculosis. I do not know much about it, but it seems to me that, if the patient had a process of that type involving the wall of the cecum, there would have been more clinical and x-ray evidence of bowel irritation. Also, the radiologist would not believe so definitely that it was something outside the bowel.

I think we need only mention various remote possibilities, such as diverticulitis of the cecum and regional enteritis.

I do not believe that the patient had true appendicitis, because I do not consider this primarily an acute inflammatory process. The location of the mass is entirely consistent with appendicitis. We do not know the interval between attacks. The last attack may have been three or four weeks before the present one. It is conceivable that the patient had one of the porky, large, chronically inflamed, low-grade inflammatory processes that occasionally involve the appendix and result in a mass in that region; such cases might very easily not present the usual findings that we associate with acute appendicitis. It is more likely that he had one of the large, dilated appendiceal tumors, such as a mucocoele, that are occasionally found at operation. It seems to me, then, that this is most easily explained by a process associated with the appendix. I do not believe that it was acute appendicitis. The other two conditions one would have to think of more seriously—and it does not make much difference how one puts them—are lymphoma, with a mass of nodes in this region, and lipoma.

A PHYSICIAN: How about a carcinoid?

DR. MCKITTRICK: That is included in the heterogeneous group of appendiceal masses.

DR. FRANCIS R. DIEUAIDE: Would a lymphomatous mass of nodes be likely to be so firm and associated with pain?

DR. MCKITTRICK: I do not know. I do not believe, however, that the symptoms were very severe. The patient went to New York, and the mass could be moved around in his abdomen. I am not paying too much attention to the tenderness.

DR. LANGDON PARSONS: As Dr. McKittrick pointed out, the history is a little unreliable, but

it is all that we could get. The patient was difficult to control.

We operated with a preoperative diagnosis of carcinoid, largely because there was a definite mass readily outlined that could be displaced toward the midline. This would not have been true of an appendiceal abscess.

DR. TRACY B. MALLORY: Do you want to describe the operative findings?

DR. PARSONS: There was a very large, dilated, nonadherent appendix, with a very firm base, which made me think that it had invaded the lower pole of the cecum and further suggested the possibility of carcinoid. The lower pole of the cecum was resected and turned in. The final diagnosis proved to be a mucocele of the appendix. An occluding web accounted for the hard and firm base.

#### CLINICAL DIAGNOSIS

Carcinoid of appendix.

#### DR. MCKITTRICK'S DIAGNOSIS

Tumor of appendix (? mucocele, ? carcinoid).

#### ANATOMICAL DIAGNOSIS

Mucocele of the appendix.

#### PATHOLOGICAL DISCUSSION

DR. MALLORY: The mass was just about twice the size of that described on physical examination—10 by 3 cm., instead of 5 by 2 cm. Its walls were very thin, and it contained clear, thin, mucous fluid. The base was completely occluded by an old scar process, as is always so in a mucocele. There was no carcinoid.

### CASE 28052

#### PRESENTATION OF CASE

A sixty-three-year-old man entered the hospital with the complaint of swelling in back of the left knee.

Two months before entry, he began to notice swelling of the posterior aspect of the upper leg just above the knee. The swelling rapidly increased in size, until at the time of entry it was as large as a grapefruit. Regularly during the night, the mass decreased to about half its volume in the daytime. The patient had no pain or other symptoms, and his general health was very good. He had lost about 10 pounds in weight during the year before entry. The past and family histories were otherwise irrelevant.

Physical examination revealed a well-developed,

well-nourished man in no acute distress. The heart, lungs, and abdomen were normal. Bilateral inguinal hernias were present, and there was moderate, symmetrical enlargement of the prostate. On the posterior aspect of the lower portion of the left thigh, there was a large, soft, smooth, slightly movable, nontender mass measuring 15 by 12 cm. It did not transilluminate, and no bruit could be heard over it. There was no limitation of motion or pain on motion of the joint.

The temperature was 98°F., the pulse 80, and the respirations 20. The blood pressure was 120 systolic, 70 diastolic.

Examination of the urine was negative. The blood showed a red-cell count of 4,860,000 with 90 per cent hemoglobin, and a white-cell count of 9450 with 73 per cent polymorphonuclears. The nonprotein nitrogen was 29 mg. per 100 cc., and the blood Hinton reaction was negative. An x-ray film of the left knee showed a round, well-defined, soft-tissue mass measuring 15 by 12 cm. behind the lower end of the femur. The mass was homogeneous, and denser than the surrounding tissue. It displaced the calcified femoral artery slightly to the right. There was no definite evidence of involvement of the bone.

An operation was performed on the fourth day.

#### DIFFERENTIAL DIAGNOSIS

DR. RICHARD H. WALLACE: Our problem is to determine the nature of a localized, rapidly growing mass of short duration, in a man who apparently was well and in whom the other findings were essentially normal.

There is nothing to suggest that the mass was inflammatory or granulomatous in origin, and from the description, the skin was not involved. The x-ray films rule out any involvement of bone, so that the origin of the swelling must have been in the intervening soft parts.

No bruit was heard, no pulsation was noted, and the calcified artery was displaced by the mass, so that we can rule out aneurysm.

One of the commonest swellings behind the knee joint is a synovial diverticulum, frequently called Baker's cyst, for the man who described it. These, however, present in the popliteal space and bulge downward into the upper portion of the lower leg. Tumors of the fibroma or neurofibroma group are too firm to fit the description in this case. Lipoma is not uncommon in this area, and I cannot rule it out; however, the growth was too rapid for one that had not become sarcomatous.

The change in size with rest in bed, with increase in the morning, suggests blood-vessel origin, or a very vascular tumor, but a superficial one of

this size should involve the skin and should not be homogeneous. The impression of a "bag of worms" is common in the hemangiomas, and both this tumor and the lymphangiomas usually decrease in size rapidly with elevation of the extremity.

Myosarcoma is found in this region and can be one of the most rapidly growing of all tumors. Its softness also fits the description, and the apparent change in size at night may have been due to its partial disappearance beneath the large muscles of the thigh when they were relaxed and the protrusion of the tumor when the patient was in the upright position, because of gravity and muscular contraction.

I believe the most likely diagnosis is myosarcoma or some mixed sarcoma with a myxomatous element.

#### CLINICAL DIAGNOSIS

Neurofibrosarcoma

DR WALLACE'S DIAGNOSIS

Myosarcoma

#### ANATOMICAL DIAGNOSIS

Liposarcoma of thigh

#### PATHOLOGICAL DISCUSSION

DR TRACY B. MALLORY. The exact diagnosis of a tumor of this character must almost always await the report of the pathologist's histologic examination. The clinician can merely speculate on the relative probabilities of the various tumors to be found in the given area. To tell the truth, it often makes little difference what the type of cell turns out to be, and the more essential decision is an estimate of the degree of malignancy. The benign tumors can be safely incised locally within their capsules, the low grade malignant tumors

are prone to recurrence if so handled and often deserve a block dissection, and the highly malignant tumors must be treated either with extensive block dissection or even with amputation.

Dr. Wallace guessed a myosarcoma, and the clinicians on the wards a neurofibrosarcoma. An incision was made over the tumor, and a rather soft, lobulated, apparently encapsulated mass was shelled out without much difficulty. In the laboratory, we made an unusual diagnosis—liposarcoma. The frequency with which this diagnosis is made varies considerably from one laboratory to another and also within the same laboratory from one five year period to another. It is not an easy tumor to recognize with certainty, since unless it is so well differentiated that fat cells of the mature or at least the fetal type are formed, one has nothing to rely on but the presence of spindle cells containing demonstrable fat. The presence of fat in a tumor cell is not particularly unusual, however, and may indicate not a metabolic activity but merely a degenerative phenomenon. Since the cells of highly malignant tumors frequently, one might almost say usually, show degenerative changes in certain areas, I must confess that I cannot interpret the presence of fat droplets in tumor cells and that I am rarely confident in making the diagnosis of liposarcoma. In this case, however, so many grades of transition from nearly adult fat cells, through multivacuolated cells of the fetal type to frank spindle cells were present that I believe the diagnosis could scarcely be doubted.

The patient made a rapid postoperative recovery, and was discharged without further treatment. A follow up note eighteen months later states that four months later a high amputation was done in another hospital, presumably for recurrence and that for the fourteen months following the second operation, he had had no further trouble.

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established in 1828

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND  
PUBLISHED UNDER THE JURISDICTION OF THE COMMITTEE  
ON PUBLICATIONS

Official Organ of  
THE MASSACHUSETTS MEDICAL SOCIETY  
and  
THE NEW HAMPSHIRE MEDICAL SOCIETY

## EDITORIAL BOARD

Joseph Garland, M.D.	Stephen Rushmore, M.D.
William B. Breed, M.D.	Henry R. Viets, M.D.
George R. Minot, M.D.	Robert M. Green, M.D.
Frank H. Lahey, M.D.	Charles C. Lund, M.D.
Shields Warren, M.D.	John F. Fulton, M.D.
George L. Tobey, Jr., M.D.	A. Warren Stearns, M.D.
C. Guy Lane, M.D.	Dwight O'Hara, M.D.
William A. Rogers, M.D.	Chester S. Keefer, M.D.

## ASSOCIATE EDITORS

Thomas H. Lanman, M.D.	Donald Munro, M.D.
Henry Jackson, Jr., M.D.	
Walter P. Bowers, M.D., EDITOR EMERITUS	
Robert N. Nye, M.D., MANAGING EDITOR	
Clara D. Davies, ASSISTANT EDITOR	

SUBSCRIPTION TERMS: \$6.00 per year in advance, postage paid, for the United States (medical students, \$3.50 per year); Canada, \$7.04 per year, Boston funds; \$8.52 per year for all foreign countries belonging to the Postal Union.

MATERIAL for early publication should be received not later than noon on Friday.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston, Massachusetts.

## PROCUREMENT AND ASSIGNMENT SERVICE

ACCORDING to a recent statement issued by the Procurement and Assignment Service, which appeared in the January 17 issue of the *Journal of the American Medical Association*, some confusion has arisen regarding the enrollment forms that were printed in the December 27 and January 3 issues of the *Journal of the American Medical Association* and in the January 1 issue of the *New England Journal of Medicine*. The form was intended only for those men *immediately* available for military service; this was implied by the first paragraph, in spite of the fact that the last two questions on the blank were such that misinterpretation inevitably followed. As a matter of fact,

it is now acknowledged that the continued registration of physicians *under thirty-six years of age who are immediately available* will suffice to meet the current needs of the military services.

The statement goes on to say that "the physical requirements for service with every military, governmental, industrial and civil agency"—the last two appear to be difficult to define—will be published shortly, so that each physician himself can determine what type of service he is physically qualified to enter. Following this, a new questionnaire and enrollment form, as well as a list of the military, governmental, industrial and civil agencies that require medical services, will be mailed to all physicians. On this form, the physician is given the opportunity to state that he is willing to volunteer his services for the duration of the emergency and to express his preference for the type of agency. The Procurement and Assignment Service will then issue a certificate of enrollment and a numbered button as evidence that the enrollee has offered to assist in the interests of national defense and that his offer has been formally recognized and accepted by the Procurement and Assignment Service.

## MEDICAL EDUCATION AND THE WAR

THE entry of the United States into the war creates an impressive series of responsibilities for the medical schools of the country. It is necessary not only to maintain but actually to increase the production of physicians to meet the needs of the armed forces, the defense industry and the civil community. Fortunately, medical students have been permitted to continue with their studies, partly through the wise point of view of the heads of the Selective Service System and partly through the admission of third-year and fourth-year students to the Medical Administrative Corps Reserve—it is hoped that the latter provision will be extended to include all medical students and even those accepted for admission by an approved school.

The total enrollment of medical schools is now larger by about 300 students than it was a year ago; however, convinced that even this is not

enough to satisfy the demand, the Association of American Medical Colleges has recommended a program of accelerated medical education. On December 29, Boston University School of Medicine, Harvard Medical School and Tufts College Medical School announced their plans to begin the next academic year on July 1, and to operate thereafter on an essentially continuous program. Such a plan, if generally adopted, will increase the production of physicians by 33 per cent during the next three years. The program has difficulties and hazards, but is certainly the safest way to bring about the needed increase.

It is the duty and privilege of medical schools to supply their share of medical officers to the fighting forces. But it is highly important that teaching staffs and research staffs be maintained at an effective level, since the calls on these services are going up and not down. Continuous operation means more teaching, and the program of defense research is growing rapidly. It is a matter for great satisfaction that in the Procurement and Assignment Service recently established in Washington there is an effective final common path for problems of medical personnel. This agency not only will deal with procurement as such but also will be concerned with the maintenance of essential services in hospitals, medical schools and other organizations.

There is room for imagination and industry in the meeting of problems imposed by war on colleges, medical schools and hospitals, throughout the successive phases of medical education. Perhaps, from these experiments of necessity, things may be learned that will help make medical education shorter, less expensive and better.

## MEDICAL EPONYM

### MÉNIÈRE'S DISEASE

The first full account of this syndrome appeared in a "Mémoire sur des lésions de l'oreille interne donnant lieu à des symptômes de congestion cérébrale apoplectiforme [Note on Lesions of the Internal Ear Giving Rise to Symptoms of Apoplectiform Cerebral Congestion]," which was printed in the *Gazette médicale de Paris* (3rd series,

16: 597-601, 1861), less than a year before the death of its author, Prosper Ménière (1799-1862), *chef de clinique* of the Paris Medical Faculty. A previous publication, "Sur une forme de surdit  grave d pendant d'une l sion de l'oreille interne [On a Form of Severe Deafness dependent on a Lesion of the Internal Ear]," had appeared in the *Bulletin de l'Acad mie imp riale de M decine* (26: 241, 1860-1861). The following is a translation of a portion of the former article.

1 An auditory apparatus that has previously been perfectly healthy may suddenly become the seat of functional disturbances consisting of noises of a variable nature, continuous or intermittent, and these noises are soon accompanied by more or less diminution of hearing.

2 These functional disturbances, which have their seat in the internal ear, may be followed by such apparent cerebral symptoms as vertigo, faintness, unsteady gait, giddiness and falling, furthermore, they are accompanied by nausea, vomiting and syncope.

3 These symptoms, which are intermittent, are soon followed by progressively serious deafness, and frequently the hearing is lost suddenly and completely.

4 Everything leads one to believe that the essential lesion behind these functional disturbances lies in the semicircular canals.

R W B.

## MASSACHUSETTS MEDICAL SOCIETY

### COMMITTEE ON MATERNAL WELFARE

#### CAUSES OF MATERNAL DEATH IN MASSACHUSETTS DURING 1940 (*continued*)

##### MEDICAL DISEASES

Forty-two deaths were caused by medical diseases (Table 1).

*Cardiac disease.* Among the 15 cases caused by cardiac disease was 1 patient with congenital heart disease who at autopsy proved to have a patent ductus arteriosus. Six days after delivery, this patient died of progressive cardiac decompensation.

Six cases were associated with cesarean section. Two of these patients had toxemia, and the circulatory failure of which they died was probably due to cardiac asthma. One patient with rheumatic heart disease had been advised against pregnancy, and when pregnant had been advised to have an abortion; she was hospitalized during pregnancy, and died shortly after operation. One patient on whom a cesarean section was done became very much worse while under treatment in the hospital. Cesarean section was performed, and death occurred a few hours later. One patient with chronic endocarditis was seen by a cardiologist at the beginning of her pregnancy and,

with his advice, was told that it was safe for her to have a baby. This patient died, six weeks after delivery, very suddenly of acute heart failure. An elderly primipara, forty-four years old, was delivered by cesarean section because of a high

TABLE 1. *Deaths due to Medical Diseases.*

CAUSE	No OF DEATHS
Cardiac disease	15
Pneumonia	14
Chronic nephritis	3
Meningitis	2
Chronic bronchiectasis	1
Acute yellow atrophy of liver	1
Pemphigus	1
Idiopathic thrombocytopenic purpura	1
Pulmonary tuberculosis	1
Tuberculous peritonitis	1
Ulcerative colitis	1
Fracture of skull	1

breech presentation, and died forty-eight hours later of cardiac dilatation and pulmonary edema.

One cardiac patient who arrived at the hospital practically moribund died fourteen hours later, undelivered. The investigator says, "As a matter of fact, this patient should have received treatment for her cardiac condition long before she became pregnant." Another patient who died undelivered was never seen early in pregnancy, and when finally seen she was not in labor and was moribund; she died immediately afterward. Another patient, at six months, arrived in the hospital with congestive heart failure and died eighteen hours later, undelivered.

One patient with chronic heart disease went through her pregnancy and delivery without difficulty, but three weeks later, when at home, she rolled over in bed, and suddenly expired. Another patient, who was known to have chronic heart disease complicated by nephritis, had had seven previous pregnancies. Abortion had been advised. This patient went through a full-term delivery; she returned to the hospital four weeks after discharge and died of cardiac decompensation and coronary thrombosis two weeks later. Another patient, in whom a diagnosis of chronic endocarditis had been made and for whom abortion had been advised, was delivered after a short premature labor by forceps and, two weeks following delivery, died of progressive heart failure.

These fatal cases of cardiac disease during pregnancy accentuate the fact that pregnancy results in death in the presence of certain complications.

*Pneumonia.* Two cases of pneumonia were associated with cesarean section. One patient developed definite pneumonia on the fourth day post partum and died a week later. An autopsy was performed, and bilateral bronchopneumonia was found. She was treated with sulfanilamide. In

the other case, pneumonia developed immediately after operation, and the patient died on the third day post partum.

Three cases of pneumonia were characterized as influenzal in type. One patient died eight days after spontaneous abortion, another eight days after delivery, and another delivered prematurely at seven months and died twelve days later. The patient with influenza following abortion did not develop the disease until five days after the spontaneous abortion, and she was dead three days later.

In the other cases of pneumonia, 1 patient had a spontaneous delivery almost at term and died four hours later; she was ill for about three days. One patient with lobar pneumonia had a spontaneous abortion at about three months and died shortly after being admitted to the hospital. Another delivered spontaneously when about five and a half months pregnant and died four days later; she was treated with sulfapyridine. One patient with lobar pneumonia died undelivered at eight months. One patient was delivered by forceps, developed a temperature immediately after delivery, and died on the seventh day; she also was treated with sulfapyridine. One patient delivered normally developed pneumonia following nitrous oxide and ether anesthesia and died two and a half days later. It is probable that the anesthetic had something to do with this death. At post-mortem examination, consolidation of all lobes of the lungs was found. Another patient, following operative delivery, died of bronchial pneumonia within forty-eight hours. Another patient, who entered the hospital with a fever and signs of pneumonia, delivered herself normally but died of bronchopneumonia twenty-six days after delivery. In the other case in which pneumonia was the cause of death, an operative delivery was performed, and fever and rales appeared the day after delivery; death occurred four days later.

So far as pneumonia is concerned, the fact that so many of these patients went into premature labor and still succumbed shows how serious this complication is in pregnancy. Obstetricians must impress on their patients that all colds during pregnancy should be treated with respect, and that any cold accompanied by fever should immediately be reported to the physician, so that the patient may be hospitalized, if necessary. In this way only may an early diagnosis of pneumonia be established and may chemotherapy be started in time to be of benefit. The incidence of fatal bronchopneumonia following cesarean section once more emphasizes the hazard of postoperative pneumonia. It should always be taken into account before ce-

sarcin section is elected. Undoubtedly, some of these cases developed pneumonia because of unsatisfactory anesthesia. It is regrettable that so many patients go into labor soon after the ingestion of a heavy meal. Vomiting of undigested food during anesthesia will sometimes cause particles to lodge in the lungs, with either collapse of the lung or subsequent pneumonia. This possibility cannot be avoided.

**Chronic nephritis** The first of the patients in this group was known to have had nephritis following scarlet fever, and after consultations with three physicians, abdominal hysterectomy was performed at about three months. The patient did well for five days and then failed and died. Autopsy showed acute yellow atrophy of the liver, as well as chronic nephritis. Another patient was delivered at about six months and died three months later of chronic nephritis. In the third case, which was one of known chronic nephritis of years' standing, the patient died undelivered at eight months.

These three cases illustrate the extreme hazard of any pregnancy superimposed on long standing chronic nephritis.

**Meningitis** One case of meningitis was due to a pneumococcus. This patient was excellently treated, but died at about five months, undelivered. An autopsy was performed. The other patient with meningitis, who died approximately six weeks after delivery, suffered a lung abscess caused by inhalation of vomitus during anesthesia, but the immediate cause of death was a meningitis of undetermined etiology.

**Acute yellow atrophy of liver** One patient died of acute yellow atrophy of the liver at about six months. Following an attack of grippé, the patient began to vomit, developed a temperature of 103°F and became jaundiced five days before death. A macerated fetus was delivered normally ten days before death.

**Pemphigus** One patient died of pemphigus, which developed along with unusually severe nausea and vomiting. During the course of the disease, she started to miscarry and was curetted, in spite of which she died two days later. There is little to be said about this case except its unusual nature.

**Idiopathic thrombocytopenic purpura** The patient with idiopathic thrombocytopenic purpura had had a normal delivery four weeks before admission to the hospital. In spite of twenty-one transfusions and the administration of cobra venom death followed. Autopsy showed multiple hemorrhages throughout all parenchymatous organs.

**Pulmonary tuberculosis** The patient who died at seven months of pulmonary tuberculosis had been admitted to a sanatorium one day before labor started. Of course, this patient never should have become pregnant.

**Tuberculous peritonitis** There was one case of tuberculous peritonitis. Miscarriage preceded abdominal operation by six weeks. The patient died five weeks after the operation.

**Ulcerative colitis** The patient who died of ulcerative colitis had been delivered normally five weeks previously. An abdominal operation preceded death.

**Fracture of skull** This patient, when seven months pregnant, was in an automobile accident and died undelivered very shortly after her admission to the hospital. Although the cause of death is not a "medical disease," the case is arbitrarily placed in this group.

## WAR ACTIVITIES

### UNITED STATES ARMY

The following medical officers entered on active duty in the First Corps Area between January 11 and January 17, 1942:

Patterson, John C., Lieut., of Boston. Manchester Air Base, Manchester, New Hampshire.  
Grulee, Clifford G., Lieut., of Boston. Fort Devens, Massachusetts.  
Maech, John V. S., Lieut., of Shelburne, Vermont. Fort Devens, Massachusetts.  
Witte, Max E., Capt., of Bangor, Maine. Fort Devens, Massachusetts.

General Hospital No 5 was recently mobilized at an Eastern Seaboard camp. This hospital, organized by the Harvard Medical School, is a continuation of Base Hospital No 5, which actively functioned in France during World War I. The officer personnel is as follows:

**Acting Director** Lieutenant Colonel Thomas H. Lannan.

**Surgical Service** Lieutenant Colonel Thomas H. Lannan, chief; Major Augustus Thorndike, assistant chief; Majors Edwin F. Cave, J. E. Dunphy, Carlyle G. Flake, John H. Harrison and Robert Zollinger, Captains Thomas W. Botsford, Thomas Cavanaugh, Stanley O. Hoerr, Lee G. Kendall, John L. Newell, T. B. Quigley, Charles P. Sheldon, Fiorindo A. Simeone, Dean W. Tanner and Richard Warren, First Lieutenants Chilton Crane, Charles L. Dimmler, Jr., Robert G. Snow and Robert R. White.

**Medical Service** Lieutenant Colonel Theodore L. Badger, chief; Major Eugene C. Eppinger, assistant chief; Majors Harold F. Corson, J. E. Greene, Stanley Kimball, Harold Levine, Charles May and Henry N. Pratt, Captains Arthur Baldwin, Richard V. Ebert, Charles P. Emerson, Joseph Frothingham, Paul Kunzel, Jack D. Myers, Carey M. Peters, Gordon A. Saunders and Roy L. Swank, First Lieutenants Samuel Asper, Henry H. Brewster, Joseph H. Burchenal and Sibley W. Hoobler.



*Laboratory Service:* Major Dale Friend; Captain Joseph H. Bragdon; First Lieutenant Richard Ford.

*X-ray Service:* Major Magnus I. Smedal; Captain Donald P. Ham; First Lieutenant Ralph C. Moore.

*Headquarters:* Captain John J. Kneisel.

*Registrar:* Majors J. Beach Hazard and Norman Vaughan, Quartermaster Corps; First Lieutenant Frederick P. Ross.

*Mess:* Major George F. Wilkins.

*Dental Corps:* Major Moses S. Strock; Captains Henry J. Carney, Harry Stone and George Sullivan; First Lieutenants Maurice Dinnerman, Gerald L. O'Neill and Maxwell Perman.

## CIVILIAN DEFENSE

### UNITED STATES OFFICE OF CIVILIAN DEFENSE

President Roosevelt has appointed Dr. George Baehr, chief medical officer of the Office of Civilian Defense, to be a member of the Health and Medical Committee of the Office of Defense Health and Welfare Services. Dr. Irvin Abell, chairman of the Committee on Medical Preparedness of the American Medical Association, is chairman of the committee, and the other members are Surgeon General James C. Magee, Surgeon General Ross T. McIntire, Surgeon General Thomas Parran and Dr. Lewis H. Weed, chairman of the Division of Medical Sciences of the National Research Council. The Office of Defense Health and Welfare Services is a part of the Office for Emergency Management, which, in turn, is part of the Executive Office of the President.

The Medical Advisory Board of the Office of Civilian Defense held a joint meeting with the regional medical officers at the national headquarters in Washington on December 8 and 9.

Coming immediately after the outbreak of war with Japan, the conference took on special importance. Mayor LaGuardia, United States Director of Civilian Defense, addressed the group briefly, urging action on two counts: organization of emergency medical field units and designation of field casualty stations in the target areas on both coasts.

The medical defense officials decided that it is necessary that blood banks, as well as collecting stations for plasma and serum, similar to those developed by the American Red Cross for the Army and Navy, be established for civilian use. It was pointed out that a supply of whole blood and of plasma and serum for use among civilians is essential, since the armed forces will not be able to release any of their supply under conditions of actual warfare.

Medical defense plans were reported to be under way in states along both seaboards in accordance with plans developed by the Office of Civilian Defense. Dr. Wallace D. Hunt, medical officer for the Ninth Civilian Defense Region, with headquarters in San Francisco, reported that the important cities of the West Coast, especially those in California, had well-developed disaster services as a result of their experiences with earthquakes, and that these were being rapidly integrated into a comprehensive civilian-defense program.

Members of the Medical Advisory Board who attended the meeting were Dr. George Baehr, New York City, chairman of the Board and chief medical officer of the Office of Civilian Defense, Dr. Robin C. Buerki, Philadelphia, Dr. Elliott C. Cutler, Boston, Dr. Oliver B. Kiel,

Wichita Falls, Texas, Dr. Albert McCown, Washington, and Dr. Huntington Williams, Baltimore. The regional medical officers present, in addition to Dr. Hunt, were Dr. Allan M. Butler, Boston, First Region, Dr. H. Van Zile Hyde, New York City, Second Region, Dr. W. Ross Cameron, Baltimore, Third Region, Dr. Judson D. Dowling, Atlanta, Georgia, Fourth Region, Dr. William S. Keller, Columbus, Ohio, Fifth Region, and Dr. Witten B. Russ, San Antonio, Texas, Eighth Region. Others present included Miss Mary Beard, director of nursing service, American Red Cross, Dr. James A. Crabtree, executive secretary, Health and Medical Committee of the Office of Defense Health and Welfare Services, Surgeon General Thomas Parran, Dr. Erval R. Coffey, United States Public Health Service, and Dr. Martha Eliot, United States Children's Bureau.

The second day was devoted to conferences with the United States Public Health Service, the Office of Defense Health and Welfare Services and the American Red Cross, whose part in the civilian-defense program was explained.

## MISCELLANY

### RÉSUMÉ OF COMMUNICABLE DISEASES IN MASSACHUSETTS FOR NOVEMBER, 1941

DISEASES	NOVEMBER 1941	NOVEMBER 1940	FIVE YEAR AVERAGE*
Anterior poliomyelitis	10	4	4
Chicken pox	1171	1270	990
Diphtheria	15	10	13
Dog bite	698	641	662
Dysentery, bacillary	46	12	39
German measles	59	34	35
Gonorrhea	332	340	453
Measles	457	985	627
Meningitis, meningococcal	14	8	5
Meningitis, other forms	7	—	—
Mumps	692	389	364
Paratyphoid infections	5	2	4
Pneumonia, lobar	193	354	233
Scarlet fever	735	481	423
Syphilis	389	407	471
Tuberculosis, pulmonary	223	143	213
Tuberculosis, other forms	28	16	21
Typhoid fever	2	6	7
Undulant fever	5	4	4
Whooping cough	710	888	703

\*Based on figures for preceding five years.

### GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Actinomycosis was reported from: Chicopee, 1; total, 1.

Anterior poliomyelitis was reported from: Beverly, 1; Brockton, 1; Easton, 1; Haverhill, 1; New Bedford, 1; Quincy, 2; Somerville, 2; Southboro, 1; total, 10.

Diphtheria was reported from: Fall River, 6; Hingham, 2; Lowell, 1; New Bedford, 1; Springfield, 3; Watertown, 1; Wrentham, 1; total, 15.

Dysentery, bacillary, was reported from: Arlington, 1; Ayer, 16; Boston, 1; Fall River, 1; Ipswich, 4; Lowell, 7; Worcester, 16; total, 46.

Encephalitis, infectious, was reported from: Danvers, 1; Sterling, 1; Westford, 1; total, 3.

Meningitis, meningococcal, was reported from: Boston, 3; Bourne, 1; Braintree, 2; Brockton, 1; Framingham, 1; Hubbardston, 1; Lynn, 2; Medford, 1; Spencer, 1; Weymouth, 1; total, 14.

Meningitis, other forms, was reported from: Boston, 1; Braintree, 1; Brockton, 1; Gloucester, 1; Northampton, 1; Salem, 1; Winthrop, 1; total, 7.

Paratyphoid infections were reported from: Lawrence, 1;

Malden, 1; Northampton, 1, Westwood, 1, Winchester, 1, total 5

Pellagra was reported from Grafton, 3, total, 3

Septic sore throat was reported from Boston, 4, Medford 3, Worcester, 1, total, 8

Tetanus was reported from Boston, 1, Cambridge, 1, August 1, total, 3

Trichinosis was reported from Haverhill, 1, Milford, 1, total, 2

Trichinosis was reported from Boston, 2, total, 2

Typhoid fever was reported from Arlington, 1, Gardner 1, total, 2

Undulant fever was reported from Adams, 1, Lowell, 1, North Brookfield, 1, Warren, 1, Wellesley, 1, total, 5

Anterior poliomyelitis continued to show an increase over the usual seasonal incidence of a nonepidemic year

Dog bite and mumps showed record high incidences, this having been the third consecutive month for dog bite and the fifth for mumps

Meningococcal meningitis showed the highest incidence for November since 1922

Bacillary dysentery, chicken pox, German measles, paratyphoid infections, pulmonary tuberculosis, scarlet fever, and whooping cough were reported above the five year averages

Diphtheria, lobar pneumonia and measles were reported below the five year averages

Typhoid fever was reported at a record low figure with the exception of that for 1939, which was equaled

Animal rabies showed record low incidence, the single reported case having occurred in Woburn

## SCHOOL LUNCHES

The Joint Committee on Health Problems in Education of the American Medical Association and of the National Education Association, recognizing the increasing importance of school lunches, adopted the following statement at its regular annual meeting, held at Atlantic City, February 25 and 26, 1941

The school lunch serves an extremely important purpose from the standpoint of nutrition and practical health education. This being the case, the Joint Committee on Health Problems in Education calls attention to certain protective sanitary measures, knowing that the carrying out of these measures will help avoid sickness resulting from contaminated food

The educational aspects of school lunches, as well as the requirements for an adequate diet, have been presented in a report by the committee (*Health Education*, 1941 edition), to which the reader is referred. The index of this report furnishes many references to the educational value of the school lunch

For the purpose of assisting further, the following additional recommendations concerning lunchroom personnel and equipment are made

(1) All persons employed in the lunchroom must be scrupulously clean in person and attire. They should be required to submit to health examinations or procedures that the health or school authorities may see fit to require

(2) The lunchroom and kitchen must be clean and as well equipped as it is possible to expect under the existing circumstances in the particular school, it should be borne in mind that many poorly equipped schools are in very special need of school lunches from the standpoint of nutrition and education

(3) There must be present and in constant use the following equipment: a stove of such capacity as will furnish abundant heat for cooking and for heating large amounts of water, a place to wash dishes where they may be scalded with water over 170°F and allowed to dry, a supply of dishes and utensils sufficient to permit good practice in the handling of food, a clean, tight cupboard for the storage of dishes and utensils used in cooking, a supply of kitchen linen or its paper substitute great enough to permit sanitary handling of the food, and an icebox or refrigerator, if at all possible

(4) Food low in price is permissible, but it must not be fermented, decomposed, frostbitten, unclear or of unsanitary quality

Milk should be pasteurized. If unpasteurized, it should be *boiled* on the premises. If powdered milk is used, it must be mixed with safe water within an hour or two of the time it is to be used

Home canned fruits are safe, but home canned meats and vegetables may be used *only* after they have been removed from the can and boiled from three to five minutes

Leftovers are never to be carried over to the next day. All food prepared must be eaten, sent home with the children or put in the garbage *the day it is prepared*

Dry-old products are not to be used if there is any ingredient which is capable of spoilage or fermentation. This precaution is particularly needed with products containing cream fillings, meringues, or non-acid dressings or sauces, such as mayonnaise, whipped cream and French dressing

(5) The housekeeping of the lunchroom and the kitchen must be above criticism. Particular attention should be given to the exclusion of flies, rats, mice, roaches and other vermin. Containers that are vermin-proof must be provided when it is impossible to eradicate these nuisances

(6) The personnel and equipment must be under the daily supervision of some responsible person trained for such work,—school physician or school nurse, principal or home economics teacher,—who will have authority to order the abatement of a condition that may be dangerous. This responsible person shall decide whether a lunchroom worker is or is not fit to work on any given day. He shall take into consideration the following points and such others as seem pertinent or necessary to ensure safety to the persons eating the school lunch

(a) Is the individual clean in person and clothing?

(b) Is there suspicion that the worker is suffering from some communicable disease? If so, he should be examined by a physician or health officer who, in turn, should inform the administrative head of the school regarding the possible transmission of the disease. He should not be permitted to return to work after sickness or absence of undetermined cause until seen by a physician

(c) Is there any infectious disease, such as scarlet fever, in the home of the worker?

(d) Is there any skin disease or discharging wound?

The close co-operation of lunchroom directors, principals and school physicians, or health officers, is required if school eating places are to be safe. These individuals working together can see that sanitary precautions are

taken and thus prevent the spread of disease through foods.

Single copies of this statement are distributed gratis by the committee through its secretary, Dr. W. W. Bauer, 535 North Dearborn Street, Chicago. Quantities will be furnished at actual cost, prices being quoted on request. Requests for free copies must be made on the official letter-heads of school systems or public-health agencies.

#### MASSACHUSETTS TUMOR DIAGNOSIS SERVICE

Dr. Paul J. Jakmauh, commissioner of public health, has announced that, in the proposed change in the work of the Collis P. Huntington Memorial Hospital, the Tumor Diagnosis Service of the Massachusetts Department of Public Health will not be interrupted and will continue to be rendered at the Huntington building. If any change of location for this service proves necessary, ample notification will be given to the physicians of the State. The Tumor Diagnosis Service has been used with continually increasing frequency by the physicians of the State; hence, it is gratifying that the change in the administration of the hospital will not interfere in any way with this service.

#### BOOK REVIEWS

*How to Prevent Goiter.* By Israel Bram, M.D. 8°, cloth, 182 pp., with 21 illustrations. New York: E. P. Dutton and Company, Incorporated, 1941. \$2.00.

This book represents the views of a very limited number of people concerning the treatment of goiter. The author has insisted for years that goiter, particularly of the exophthalmic type, can be successfully treated by so-called "conservative medical treatment." The work is dedicated to "the men and women of science who seek to clarify the mysteries of glandular function," an undertaking, one must admit, of no small magnitude. In the preface, it is stated that the author has been asked from many quarters to address the general public on how to prevent goiter, which is the stated purpose of the book. It presents to the lay public a very reasonable discussion of the various types of thyroid disease.

There are a number of statements in the book with which one who has had any considerable experience with thyroid disease would disagree. One statement under the question of the use of iodine is: "While iodine in the treatment of exophthalmic goiter usually yields temporary benefit, it may give rise to a secondary harmful reaction which may endanger life." In a large experience with goiter, the reviewer has never observed such a condition.

Likewise, the statement is made that the author has seen the employment of iodine for a long time "productive of such enormous swelling of the thyroid gland as to result in almost fatal choking from pressure." In an experience now dealing with literally thousands of these cases, the reviewer has never seen such a situation.

In Chapter 13, "Prevention of Exophthalmic Goiter," under the heading, "The Type of Humanity Involved," the following statements are made: "Prior to the development of the disease [exophthalmic goiter] to which we may be susceptible, we may appear quite normal in the every-day sense of the word. Yet on careful examination there are certain earmarks by which one may distinguish susceptibility to tuberculosis, to diabetes, and to other diseases, including exophthalmic goiter. A timely recognition of the type of constitution of the individual may enable us to increase resistance to the malady in question."

This is typical, in the reviewer's mind, of many of the vague statements made by the author in this book and in his writings for professional consumption. Under the heading, "How to Reduce Susceptibility," occur further examples of the indefinite, intangible factors that those who are supposedly susceptible to this disease should avoid.

Under the heading, "High Lights in Treatment," is the following: "A successful outcome depends on individualization. While one patient may improve through the use of cold baths, in another these may produce nervousness. While many patients get along very well on a non-flesh dietary, most require the occasional addition of lamb chops, fish or fowl in order to avoid monotony of diet." Repeatedly in this monograph, one finds instructions to do this in one case and that in another. Here also is contained the statement, "Treatment must be broad and comprehensive, and if begun early, at least 90 per cent of patients will be rewarded by permanent restoration to health and happiness."

One can only say as this book, with its numerous photographs of before and after, is reviewed that it represents views that are not universally held. One cannot miss the implied criticism of so many thousands of people who have submitted themselves to surgery, even with its low mortality rate, and are satisfied with the results if as the author states, it is possible to accomplish the same things without surgery. In answer to the natural question that arises concerning the substantiation of the statement contained in this book, a method that can accomplish all that is promised will, if it is worth while, win its way with the public in spite of opposition, disagreement and everything else. When methods of treatment, surgical and those in this book, have been before the public for so many years, and when so few people accept and support the latter and more agreeable measures, it must be said that the verdict has been rendered by an intelligent and critical public.

*Native African Medicine, with Special Reference to Its Practice in the Mano Tribe of Liberia.* By George W. Harley, M.D. 8°, cloth, 294 pp., with 2 illustrations. Cambridge, Massachusetts: Harvard University Press 1941. \$3.50.

Dr. Harley, a skilled anthropologist and a missionary physician, spent many years in West Africa. In addition to his work as a missionary, he has made a very careful study of certain tribes, their religious and medical rituals, their methods for treating disease, and other matters of similar interest. The facts, as well as the theories behind the practice of medicine by the native African Negro, are clearly set forth in this book—a monograph of great interest to anthropologists and students of the history of medicine. Dr. Harley has analyzed the various drugs and poisons used by the natives and estimated their effectiveness in the treatment of diseases. He found that in ninety-nine diseases and pathologic conditions, the treatment was at least partially rational in most; moreover, he classified 65 per cent of the remedies used as clearly rational. The diseases were principally those with visible lesions, whereas those treated with magic were either serious or chronic or those that appeared with startling suddenness. The author concludes that there is evidence pointing to a tremendous number of valuable remedies used in African medical practice. The importance of this book, from the medical point of view, lies in his evaluation of the remedies that he saw used, as well as in his suggestions of their effectiveness. The volume, which is a skillfully written monograph recommended by the History of Science Society, can be endorsed as an outstanding study of the subject.

(Notices on page viii)

# The New England Journal of Medicine

Copyright, 1942, by the Massachusetts Medical Society

VOLUME 226

FEBRUARY 5, 1942

NUMBER 6

## THE USE AND ABUSE OF THE ELECTROCARDIOGRAM IN MEDICAL PRACTICE\*

H. M. MARVIN, M.D.†

NEW HAVEN, CONNECTICUT

SINCE it is impossible to discuss briefly and adequately either the uses or the abuses of the electrocardiogram, my comments must be restricted to a few of the major aspects. Because the value of electrocardiography is more widely recognized than its limitations, I shall devote more attention to the latter. I shall try to consider matters that lie within the range of my personal knowledge and experience, or those that are accepted as established facts by acknowledged authorities in this field; any apparent dogmatism in my statements is due solely to limitations of time.

\* \* \*

I shall consider very briefly a few of the more important ways in which electrocardiography can be of value in diagnosis and treatment; this discussion is not concerned with its advantages in laboratory research. I think one might mention first that this procedure is acknowledged to be the one certain method for the absolute identification of irregularities of the cardiac rhythm. It is true that electrocardiograms are often unnecessary for this purpose, for after several years of experience it is possible to identify most arrhythmias by means of auscultation alone. But there are circumstances in which clinical recognition is difficult or impossible, even for those with long experience, and at such times the electrocardiogram usually reveals the diagnosis immediately and clearly. If the arrhythmia is a complicated one, such as auricular fibrillation with a rapid ventricular rate complicated by frequent ectopic beats and short paroxysms of tachycardia, its certain identification is usually impossible without the aid of the electrocardiogram. Examples of this could be multiplied indefinitely, but the fact is too well established to require further discussion. This use of the

electrocardiogram is possibly its most significant one in clinical medicine.

Furthermore, the electrocardiogram occasionally gives valuable indications that the heart has been involved in the course of systemic diseases. It is particularly useful in rheumatic fever, diphtheria and trichinosis; in any of these diseases, it may provide the first—and indeed the only—evidence that the infecting organism or the toxin has affected the heart. It is probably justifiable to say that every patient who has one of these conditions should have electrocardiograms taken at frequent intervals, at least during the acute phase of the disease.

Again, these graphic records are usually of great value in the recognition of acute myocardial infarction, which is due in most cases to coronary arterial thrombosis. They often make it possible to identify cases of old, and previously unrecognized, myocardial infarction, but these are usually less important because the necessity for immediate and careful treatment is less urgent. In most cases, the curves not only reveal that there is a fresh infarct in the wall of the heart, but also point fairly clearly to the exact area involved, although I question whether this is clinically so essential as it was considered several years ago. Blumgart and his colleagues<sup>1</sup> have shown that coronary thrombosis with or without myocardial infarction has already occurred in many patients whose histories indicate nothing more than mild or moderate anginal pain on effort. It is now known that the electrocardiograms of many patients who are just beginning to experience such pain display the characteristic and progressive changes of recent myocardial infarction, and thus provide clear indications for the proper treatment at the proper time.

Occasionally, the electrocardiogram reveals clear evidence of digitalis intoxication that was unsus-

\*Presented before the New England Postgraduate Assembly, Cambridge, Massachusetts, October 29, 1941.

†Associate clinical professor of medicine, Yale University School of Medicine, and attending physician, New Haven Hospital.

pected by careful and competent physicians. Although in some of these cases a critical review of the history indicates that overdosage should have been suspected, in others the dose has not been large and the usual symptoms of toxicity have been absent. The great significance of this diagnosis perhaps needs no emphasis, but it is well exemplified by a patient whom I saw recently: a sixty-five-year-old woman whose chief symptoms were physical weakness and profound depression, with occasional hallucinations and periods of disorientation. She had been in bed for several weeks, and the mental confusion was increasing; the possibility of admitting her to an institution for the treatment of mental disease was being seriously considered. She had taken digitalis for some weeks in doses of 0.1 gm. ( $1\frac{1}{2}$  gr.) daily. Physical examination was entirely negative except for a third sound at the apex of the heart. The correct diagnosis—digitalis intoxication—was not suspected until the electrocardiogram was obtained; this showed incomplete auriculoventricular heart block, with a marked delay in auriculoventricular conduction, and depression of the RST segments. The third heart sound was due to the fact that the audible auricular contraction fell relatively early in diastole, and the mental symptoms were caused entirely by digitalis, since they disappeared completely after the drug was discontinued and reappeared in the same form when digitalis was resumed. This effect of digitalis is not especially uncommon in older people and is occasionally produced by relatively small doses, which may not affect the electrocardiogram so clearly as in this case. In another case, an excellent cardiologist made an unhesitating diagnosis of auricular fibrillation on the basis of auscultation of the heart when the condition was actually paroxysmal ventricular tachycardia, with alternation of upward and downward ventricular deflections due to severe digitalis poisoning. Fortunately, an electrocardiogram was obtained before the patient had received the large dose of digitalis that was prescribed. This mistake, which might easily have been made by anyone, emphasizes the necessity of securing these curves before proceeding with treatment, whenever it is feasible to do so.

Of less significance than any of the foregoing, but nevertheless not to be ignored completely, is the help that may be derived from the electrocardiogram in the recognition of structural lesions. Among the lesions that are sometimes reflected in changes in the curves are acute pericarditis and acute pulmonary infarction. I do not wish to place great emphasis on the role of the electrocardiogram in either of these conditions, be-

cause the changes are by no means constant and the diagnosis is often so clear from the clinical evidence alone that an electrocardiogram is unnecessary. Furthermore, there is not complete agreement as yet on the electrocardiographic pattern that should be accepted as indicative of pulmonary infarction, since this lesion may change the curves in a variety of ways. In chronic constrictive pericarditis, the electrocardiogram may provide evidence regarded by some as confirmatory, but it is not specific and the diagnosis should rest largely on other signs. Considerable emphasis has been placed on the presence of axis deviation of the electrocardiogram to the right or the left in the diagnosis of structural lesions that impose added work on the right or left ventricle. The classic association is that of right-axis deviation with mitral stenosis and of left-axis deviation with aortic valve lesions or arterial hypertension. But these matters seem to me of relatively little consequence, since axis deviation may depend on many factors besides ventricular enlargement, and the diagnosis of valvular lesions should be made by auscultation without great difficulty and with considerable confidence.

There is time to mention only one other circumstance in which the electrocardiogram may prove to be of great value. Those who specialize in the field of cardiovascular disease often have occasion to see people who are disturbed and apprehensive because of their belief that they have heart disease, when as a matter of fact they do not. Sometimes, this fear is based on unimportant symptoms, such as slight superficial stabs of discomfort over the precordium or the consciousness of occasional premature beats; sometimes—and far too often—on injudicious comments by physicians or nurses. It is unnecessary to mention the more serious conditions known as neurocirculatory asthenia and cardiac neurosis. In the treatment of such patients, it is imperative to convince them that everything possible has been done to ascertain the condition of the heart. An electrocardiogram is an essential part of the examination of every such person, and it may be a comfort both to him and to the physician to know that it is a normal one. I do not for one moment forget the well-known fact that a normal electrocardiogram does not exclude heart disease and may actually be obtained from patients who have heart failure; also I do not forget that a normal electrocardiogram, when combined with a negative cardiac history and negative physical and fluoroscopic or x-ray examinations, is vital additional evidence that strengthens the physician's belief that the heart is free from serious disease. This may be of psychologic value only, but

it is psychologic treatment that such patients need. I have known many patients—among them, a considerable number of physicians—whose burden of fear and anxiety has been greatly lightened by the knowledge that the electrocardiogram was perfectly normal.

This very hasty and incomplete survey of the contributions that the electrocardiogram may make to clinical medicine might be summarized by the statement that it identifies with certainty all known irregularities of cardiac rhythm, it may provide the first sign that the heart has been invaded by disease, it often shows in unmistakable terms that myocardial infarction has occurred, it may reveal unsuspected digitalis intoxication or serious poisoning, it sometimes provides help in the recognition of structural lesions in the heart or lungs, and it is often of great psychologic value in the examination of those who believe they have heart disease but whose hearts are actually normal.

\* \* \*

Having mentioned briefly some of the possible contributions of the electrocardiographic method to medical practice, I must now concede that the present widespread employment of this method may actually be doing more harm than good, if one excludes its use in large hospitals. I make this statement quite soberly, and shall attempt briefly to indicate some of the reasons that I believe to be responsible for this anomalous and deplorable situation. My comments do not apply to most large hospitals, and not at all to those investigators, teachers and clinicians who have brought the knowledge of electrocardiography to its present high level and are utilizing it daily in their work.

It may simplify the discussion of this matter if one remembers that abnormalities in the electrocardiogram, broadly speaking, consist of those associated with the arrhythmias on the one hand, and those in the conduction intervals and the ventricular complexes on the other. In general, the serious errors of interpretation are confined to the latter and not to the diagnosis of arrhythmias, although even these are often unidentified or misnamed. It is the changes in the ventricular complex, including its terminal portion, that are mainly responsible for the gross misuse of a valuable diagnostic procedure. And the first statement I wish to make is that the average practitioner who undertakes to interpret electrocardiograms does not realize, or refuses to believe, that the changes in this part of the curve have no specific significance whatever, with the single exception of changes associated with myocardial infarction. To express it otherwise, the alterations in the conduction intervals or in

the QRS complex and T wave on which he places emphasis in his diagnosis of coronary sclerosis or myocardial damage are not indications of any specific lesion in the heart, and may indeed be due to many causes other than heart disease. If this one truth could be accepted and remembered, most of the troubles with the method would end.

In the second place, the electrocardiogram almost never gives any helpful information about the functional state of the heart muscle, although thousands of physicians request such a record in the firm belief that the one who interprets the electrocardiogram will be able to determine exactly how much or how little activity the patient may be permitted. Actually, a very brief experience proves its uselessness in this respect and indicates what might be termed its positive and negative failure to portray the functional condition of the heart. For it has long been established beyond all possibility of doubt that the electrocardiogram may be perfectly normal in many patients whose hearts are seriously diseased, as in anginal or congestive heart failure. One may say with some confidence that the occurrence of acute myocardial infarction is about as clear evidence of coronary atherosclerosis as one can usually obtain during life, yet it is known that the conspicuous changes in the curve that often result from this condition may disappear wholly within a few months and thus leave the electrocardiogram normal. There is general agreement that a considerable percentage of patients who suffer from severe and unmistakable angina have normal curves, yet their hearts are abnormal. To indicate the failure of the electrocardiogram in the opposite direction, I need only state that certain well-marked alterations, often interpreted as indications of myocardial disease, may be found in the curves of persons who present no other signs of heart disease and who live for many years with no impairment of cardiac function and with no further change in the graphic records. Therefore, if it is known that a normal electrocardiogram may be obtained from a patient with advanced heart disease, and a distinctly altered curve from a person who has no clinical signs of heart disease, how can one possibly ask that the electrocardiogram reveal the functional condition of the myocardium? It is manifestly impossible, yet it is being asked scores of times every day.

A third misconception responsible for many errors is the fairly common belief that the electrocardiogram is an accurate quantitative indicator of the amount of digitalis active in the heart at a given moment. It is very difficult indeed to persuade some experienced clinicians that the record

will not tell precisely whether the patient needs a little more digitalis, a great deal more digitalis, or whether he has received a little too much and is on the verge of intoxication. As a matter of proved fact, the electrocardiogram will do no such thing. The curves from one patient may display marked changes preceding or accompanying the clinical signs of therapeutic effects, those from a second may show no changes (or very slight ones) when the patient is known to be fully digitalized, and those from a third may show only trivial alterations when there are clear signs of digitalis intoxication, as manifested by headache, nausea and vomiting. There are probably occasional cases in which the electrocardiograms give help concerning the administration of digitalis; it is quite certain that there are many in which they give none, and some in which they may actually be misleading if one is so foolish as to rely on these curves alone for guidance. The recent careful study of Geiger and his associates<sup>2</sup> has shown that depression of the ST segments, long regarded as an invariable effect of the administration of digitalis in therapeutic doses, occurred in less than half their digitalized patients. They also found—and this is perhaps of even greater consequence—that the onset and progression of such changes were not constant and were not quantitatively related to the amount of the drug that had been administered. Their study, which confirms the experience of many careful observers, indicates the impossibility of using the electrocardiogram as an index of the *degree* of digitalization.

There is another way in which these curves are often misused: some physicians still attempt to secure information about the prognosis from the electrocardiogram, although it has been shown again and again that this is usually impossible. In acute diphtheritic myocarditis, rapidly progressive changes in the ventricular complexes may justify the fear that death is imminent, and in occasional cases of acute myocardial infarction, similar progressive alterations may arouse the suspicion that the area of injury in the heart is larger and more serious than the clinical signs indicated. But even in these acute conditions, the graphic records must be interpreted in the light of the clinical evidence, while in chronic heart disease it is the clinical picture and laboratory data as a whole that must be used as the basis for estimating the prognosis.

Finally, and this is really but an amplification of my first criticism, misinterpretation of the electrocardiogram is responsible for a very large number of unjustified diagnoses of heart disease. The diagnosis of coronary disease is being made today

almost as freely as that of vitamin deficiency, and with far less justification. But I doubt if many physicians other than those who specialize in this particular field realize the extent of this error or the tragic consequences that often follow. I am speaking with deliberate conservatism when I say that every week scores, if not hundreds, of normal healthy subjects are restricted in their activities and made to suffer needless apprehension because of diagnoses of heart disease based on *minor* changes in the electrocardiogram alone, in the absence of all supporting clinical evidence. This statement is amply warranted by my own experience, but I do not limit it to my practice or to the State of Connecticut. Like all others who specialize in this restricted field, I see many curves taken in various parts of the United States, brought to me for the most part by patients who have been condemned to a life of semi-invalidism solely because of changes in the electrocardiogram. In most cases, these changes consist of such unimportant alterations as minimal slurring of the R or S wave in one lead, low voltage of the ventricular deflections in one or two leads, and the presence of a large Q wave or inverted T wave in Lead 3. My friends and colleagues in other cities tell me that their experiences are exactly similar to mine. But perhaps the best indication that this misuse of the method is not confined to one part of the country is the fact that the American Heart Association has received letters from leaders in the cardiovascular field in the East, the South, the Midwest and the far West, asking if some board cannot be established for the sole purpose of certifying those physicians who are competent to interpret electrocardiograms. And why? Because they have been appalled at learning how many wholly untrained and incompetent physicians have purchased electrocardiographs and are using them daily in their offices, with serene confidence in their ability to distinguish between the important and the unimportant changes in the curves. In many cases, their erroneous diagnoses would be merely ridiculous if they did not so often lead to tragedy in the lives of their patients.

I believe one of the principal reasons why the electrocardiographic method is doing widespread harm today is that many physicians overemphasize its value and underestimate its limitations. They confidently expect it to accomplish much the same things that a surgeon expects of an exploratory laparotomy: that it will disclose the nature of the pathologic process, reveal its exact location and extent, and tell a great deal about the immediate treatment and prognosis.

They fail to realize that it is purely a laboratory procedure, comparable in many respects with a roentgenogram or a leukocyte count. As such, the electrocardiogram is to be interpreted merely as one finding among many, and in the light of all the clinical evidence and other laboratory tests. With the exception of the arrhythmias and some cases of acute myocardial infarction, it is reprehensible to attempt an interpretation of the elec-

trocardiogram without knowing the clinical findings and the clinical diagnosis

303 Whitney Avenue

#### REFERENCES

- 1 Blumgart H L, Schlesinger M J and Davis D. Studies on the relation of the clinical manifestations of angina pectoris, coronary thrombosis and myocardial infarction to the pathologic findings, with particular reference to the significance of collateral circulation. *Am Heart J* 19:191, 1940
- 2 Geiger A J, Blancy, L F and Druckemiller W H. A quantitative electrocardiographic study of digitalization. *Am Heart J* 22:230-244, 1941

## RIGHT-UPPER-QUADRANT PAIN ON EFFORT: AN EARLY SYMPTOM OF FAILURE OF THE RIGHT VENTRICLE\*

NORMAN H BOYER, MD,<sup>†</sup> AND PAUL D WHITE, MD<sup>‡</sup>

BOSTON

**P**AINFUL congestion of the liver at rest, due to sudden stretching of its capsule, during right-sided heart failure is frequently encountered. This must be regarded, however, as a fairly advanced stage of failure, just as dyspnea at rest must be considered a distinctly advanced stage of left-sided heart failure. Even as the stage of constant pulmonary engorgement is frequently preceded by a period during which additional loads put on the left ventricle may result in temporary flooding of the lungs with blood, so, we believe, there is a period of weakness of the right ventricle when a greater burden will result in temporary congestion of the liver. This organ forms a capacious blood reservoir and serves as a pool for the general venous circulation in the early stage of right ventricular failure. Patients are not uncommonly seen in whom the liver is enlarged, but in whom there is little or no obvious venous distention or increase in venous pressure, both in the early stages of failure and during the course of recovery from advanced failure.

In the case that initiated our interest in this subject in 1938, the patient was a twenty-one-year-old student who had always been well—except for attacks of rheumatic fever at the ages of five, fourteen and fifteen years—until six weeks prior to admission, when he began to feel poorly and to tire easily. Two weeks later, he went to his home, at an elevation of 8000 feet, where he became miserable with palpitation, upper abdominal discomfort and anorexia. He was digitalized at that time, but without much benefit. The striking thing in the history on admission to the hospital was that the only specific complaint was a "tight feeling"

in the right upper quadrant that came on regularly while he was walking up one flight of stairs at average speed and disappeared with rest. Physical examination revealed mitral stenosis, slight aortic regurgitation and auricular fibrillation. The only sign of heart failure at this time was a tender liver edge palpable two fingerbreadths below the costal margin. During the next two months, the patient developed progressive signs of right-sided heart failure, with distended neck veins and edema, and died with intractable congestive failure and rheumatic fever.

Following this experience, 3 more patients were encountered in whom the initial symptom of heart failure was pain in the right upper quadrant coming on with exertion and disappearing with rest. One patient was a forty-nine-year-old Negro whose chief complaint was right-upper-quadrant pain on effort. In this patient, an arrhythmia with tachycardia had been present for some years, and electrocardiography showed this to be auricular flutter with an auricular rate of 280 and an auriculoventricular block varying from 2:1 to 4:1, so that the ventricular rate averaged about 100 at rest. The electrocardiogram also showed inverted T waves in Leads 1 and 4, with a tendency toward right axis deviation. The blood Hinton reaction was positive, but there were no heart murmurs, and x-ray examination showed no obvious abnormality of the aorta or significant cardiac enlargement. The pulmonary second sound was not accentuated. There was calcification at the roots of the upper and lower lobes of the right lung, with considerable emphysema and diaphragmatic adhesion on the right. Albuminuria was constant, and there was moderate anemia. The arterial blood pressure was 120 systolic, 80 diastolic. The venous pressure measured 200 mm at first, but under treatment by digitalis, with reduction of the ven-

\*Presented before the New England Heart Association, Massachusetts General Hospital, December 16, 1940.

<sup>†</sup>Instructor in medicine, Boston University School of Medicine; assistant physician, Evans Memorial Hospital.

<sup>‡</sup>Lecturer in medicine, Harvard Medical School; physician, Massachusetts General Hospital.



tricular rate to 70 by an increase in the grade of block, it dropped to 96 mm. The liver was slightly enlarged. The patient was discharged in a much improved condition, with a diagnosis of auricular flutter and systemic venous congestion.

The etiology of this patient's heart failure remains obscure. At first, it was attributed to the effect of prolonged tachycardia, and this, in part at least, is doubtless the correct answer. He has since been followed for several months during which his failure has become progressively more marked, despite control of the ventricular rate by means of digitalis. The absence of signs pointing to pulmonary hypertension makes the usual causes of cor pulmonale unlikely. Recent x-ray evidence of increase of the heart shadow to the right, in addition to the electrocardiographic abnormalities, makes it probable that the chambers of the right side of the heart are involved primarily, whether from preponderant fatigue due to the tachycardia or from some unknown abnormality. Whatever the cause of the circulatory failure, the liver congestion was clear — at first, paroxysmal and, later, persistent.

Measurements of the circulation time and venous pressure were made on this patient before and after exercise. The exercise consisted in walking over the standard two-step stairs described by Master<sup>1</sup> at the rate of one trip in four seconds for a period of two minutes. It will be appreciated that this is only a very moderate grade of exercise, amounting to the ascent of two flights of stairs in a rather leisurely manner. Paraldehyde was the test substance used for measuring the circulation time from antecubital vein to pulmonary capillaries, the normal values by this method ranging from 3 to 9.5 seconds.<sup>2</sup> The venous pressure was measured by the direct method of Moritz and von Tabora.<sup>3</sup> The response of the venous pressure to exercise in normal persons is somewhat variable, depending on several factors — principally on whether the pressure is measured in an exercised or unexercised limb. According to McCrea, Eyster and Meek,<sup>4</sup> the pressure in the hand veins rises during and following exercises involving the use of the leg muscles. The rise may be several times the control value and may persist for over five minutes after cessation of the exercise. The extent of the rise depends in part on the severity of exercise and in part on the training of the subject. We have confirmed the finding of a rise in venous pressure following exercise in two normal persons. The finding of a comparable increase in the venous pressure after exercise in the patient with right-upper-quadrant pain and in another patient with a moderate degree of right ventricular failure

was of considerable interest. The response of the venous pressure to exertion thus does not necessarily provide a crucial index of the competency of the right ventricle, although this unexpected finding deserves further study.

The behavior of the circulation time proved to be more helpful in separating patients with normal hearts from those with impaired myocardial function. Figure 1 shows the results of the

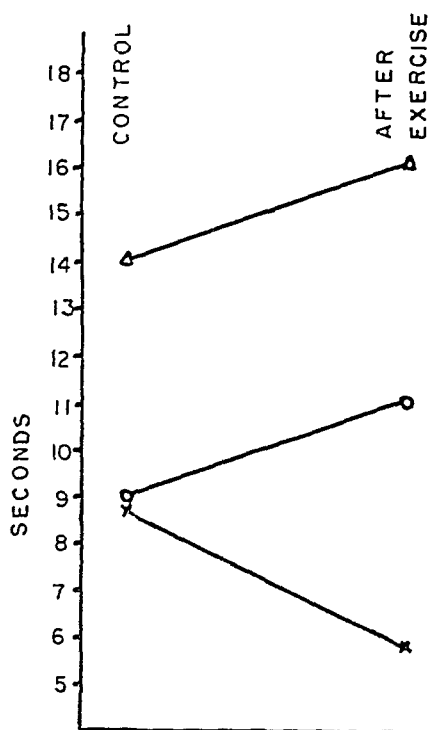


FIGURE 1. *Arm-to-Lung Circulation Time Before and Immediately Following Exercise.*

*The upper figures (Δ—Δ) are those of a patient with moderately advanced right ventricular failure; the middle (o—o), those of a patient with paroxysmal right-upper-quadrant pain; and the lower (x—x), those of a normal control.*

circulation-time tests in the patient with right-upper-quadrant pain cited above, in a patient with a moderate degree of right ventricular failure on the basis of long-standing mitral stenosis but with no history of abdominal pain, and in a normal subject. Since it has already been established that the circulation time regularly decreases in normal persons after exercise,<sup>5, 6</sup> the data on one normal control subject has been included to indicate that the method used is applicable to the data derived from other methods. It will be seen that in the normal subject the arm-to-lung time before exercise was a little less than 9 seconds, and that after exercise it had shortened to a little less than 6 seconds. The patient with clinically evident right-sided failure began with a definitely prolonged

arm-to-lung time,—that is, 12 seconds,— which was further prolonged to 16 seconds after exercise. The patient with the syndrome of right-upper-quadrant pain had a normal circulation time to begin with, but after exercise it rose to a definitely abnormal level. This abnormal reaction to exercise can be interpreted as meaning inability of the right ventricle to cope with the increase in venous return, with resultant slowing of the blood flow from the unexercised limb. Palpation of the patient's liver before and after exercise revealed no demonstrable change.

It has been our experience, as well as that of others, that the arm-to-lung time, although de-

dates for it by virtue of long-standing pulmonary hypertension secondary to mitral stenosis or, in a few cases, to left ventricular failure.

This direct questioning showed the reason why the symptom has not been emphasized heretofore and why it was mentioned in only 1 of 1000 case histories of congestive heart failure recently reviewed at this hospital. Only rarely was it of any severity, and it was frequently so overshadowed by subsequent developments as to lose significance in the patient's mind. The character of the pain was usually described as dull or aching in type, but also not infrequently as a feeling of tension or tenderness, and occasionally as quite

TABLE 1. *Characteristics of Intermittent Right-Upper-Quadrant Pain as an Early Symptom of Right Ventricular Failure.*

CASE NO.	AGE	SEX	CARDIAC LESION	TYPE OF PAIN	DEGREE OF PAIN	PRECIPITATING FACTOR
	37.					
1	39	F	Rheumatic heart disease, with mitral stenosis	Aching	Mild	Exertion
2	38	M	Rheumatic heart disease, with mitral stenosis	Aching	Mild	Exertion
3	47	F	Rheumatic heart disease, with mitral stenosis	Aching	Moderate	Exertion
4	31	F	Rheumatic heart disease, with mitral stenosis	Sharp	Moderate	Cough
5	22	M	Rheumatic heart disease, with mitral stenosis	Aching	Mild	Exertion
6	38	F	Rheumatic heart disease, with mitral stenosis	Aching	Moderate	Exertion
7	29	F	Rheumatic heart disease, with mitral stenosis	Sharp	Moderate	Unknown
8	38	F	Rheumatic heart disease, with mitral stenosis	"Tired"	Mild	Exertion
9	21	M	Rheumatic heart disease, with mitral stenosis	Tension	Mild	Exertion
10	26	F	Rheumatic heart disease, with mitral stenosis	Sharp	Moderate	Exertion
11	33	M	Rheumatic heart disease, with mitral stenosis	Sharp	Moderate	Exertion
12	37	M	Rheumatic heart disease, with mitral stenosis	Aching	Mild	Exertion
13	49	M	Rheumatic heart disease, with mitral stenosis	Aching	Moderate	Exertion
14	61	M	Coronary heart disease	"Tender"	Severe	Unknown
15	67	M	Hypertension	Sharp	Moderate	Exertion
16	48	M	Aortic stenosis	Aching	Moderate	Exertion
17	55	M	Hypertension	Aching	Severe	Exertion
18	49	M	Long-standing auricular flutter	"Dragging"	Moderate	Exertion

signed to measure the right-sided circulation, may be affected by congestive changes in the lung capillaries. Some patients with mitral stenosis therefore show prolongation of the paraldehyde time following exercise, even in the absence of significant heart failure. We were fortunate in encountering this patient with the signs of heart failure limited to the systemic circuit in whom changes of blood velocity, as measured by paraldehyde, could be evaluated in terms of efficiency of the right ventricle alone.

The following hint of the awareness of such a symptom as that under discussion was found in Vaquez's<sup>7</sup> book: "The functional disorders [of the liver] begin as subjective symptoms, slow digestion, belching of gas, bloating of the stomach, and a sensation of tension in the epigastrium and hypochondria which is aggravated by standing or walking." No other reference to this symptom on effort has come to our attention.

We have attempted to gather information on the incidence of this symptom and have found that in a small group of selected patients, numbering about 40, it was present in 18. The group selected for questioning were patients who either had definite right-sided failure at the time or were candi-

sharp. The commonest precipitating factor was walking, but the pain was induced in 1 patient by paroxysms of coughing, and in 2 patients, although the pain was paroxysmal, no precipitating cause could be elicited (Table 1). It disappeared, as exertional dyspnea does, after a few moments of rest.

The duration of the period of recurrence of this symptom seems to be short, usually a matter of two or three months, because, on the one hand, the patient regains some of his lost reserve or, on the other, failure progresses so as to stretch the liver capsule, when the probable mechanism of the symptom is lost. When 1 patient (Case 12) was questioned, he had only well-compensated mitral stenosis, but he was able to recall very clearly having gone through a period about four years previously when right-upper-quadrant pain on effort had been present. At that time, he was leading a very active life and doing moderately hard work. He consulted a physician and learned for the first time that he had rheumatic heart disease. He took his physician's advice to decrease his activity; the abdominal pain disappeared and had not recurred during the ensuing four years. Unfortunately, most of the other patients progressed to frank con-

gestive failure. Whether they might also have been spared advanced failure by the proper recognition and treatment of their early symptoms cannot be answered with confidence, but it seems likely that some, at least, might have been. Obviously, when a patient is precipitated into acute failure by, for example, auricular fibrillation with tachycardia, he may not pass through this stage of paroxysmal liver engorgement, but will at once present the more familiar picture of prolonged right-upper-quadrant pain and tenderness.

### SUMMARY AND CONCLUSIONS

We have recently encountered 4 patients in whom right-upper-quadrant pain, precipitated by exertion and relieved by rest, has been the presenting symptom of early right-sided heart failure. It is evidently due to acute congestion of the liver and is comparable to dyspnea on effort in early left-sided heart failure.

Direct questioning of a group of 40 patients

who already had clinically evident right-sided failure, or were likely candidates for it, revealed that the pain had been present at some time in about 45 per cent. It is a symptom to which the patient rarely attaches much significance, since it is usually of little severity and is overshadowed by more uncomfortable symptoms.

If the symptom is sought as diligently as the history of dyspnea on exercise, it may be found to be a fairly common and reliable warning of early weakness of the right ventricle.

### REFERENCES

1. Master, A. M. Two-step test of myocardial function. *Am. Heart J.* 10:495-510, 1935.
2. Candel, S. Determination of the normal circulation time from the antecubital vein to the pulmonary capillaries by a new technique. *Ann. Int. Med.* 12:236-243, 1938.
3. Moritz, F., and von Tabora, D. Über eine Methode, beim Menschen den Druck in oberflächlichen Venen exakt zu bestimmen. *Deutsches Arch. f. klin. Med.* 98:475-505, 1910.
4. McCrea, F. D., Eyster, J. A., and Meek, W. J. The effect of exercise upon diastolic heart size. *Am. J. Physiol.* 83:678, 1928.
5. Fishberg, A. M. *Heart Failure*. 788 pp. Philadelphia: Lea and Febiger, 1937. P. 50.
6. Best, C. H., and Taylor, N. B. *The Physiological Basis of Medical Practice*. 1684 pp. Baltimore: William Wood & Co., 1937. P. 229.
7. Vaquez, H. *Diseases of the Heart*. Translated by G. F. Laidlaw. 743 pp. Philadelphia: W. B. Saunders Co., 1924.

## CONGENITAL HYDRONEPHROSIS IN THE LOWER HALF OF A DOUBLE KIDNEY\*

### Report of a Case

SIDNEY FEYDER, M.D.,† AND CLYDE L. DEMING, M.D.‡

NEW HAVEN, CONNECTICUT

**M**ASSIVE congenital hydronephrosis filling half the abdomen and associated with reduplication of the ureter and renal pelvis has heretofore not been recorded. It is recognized that reduplication of the ureter wholly or in part and slight or moderate hydronephrosis are frequently encountered at routine cystoscopic examinations. However, a hydronephrosis filling half the abdomen from the diaphragm down into the bony pelvis is a rare condition. Cystic tumors large enough to displace the intestines to the opposite side of the abdomen present intriguing diagnostic problems. The following case was completely and accurately diagnosed preoperatively.

### CASE REPORT

G. D. (B 8902), a 5-year-old boy, was admitted to the Pediatric Service of the New Haven Hospital for study because of an abdominal mass discovered by a physician during a routine physical examination. The patient was said to have always had a protuberant abdomen, which

had been growing steadily larger. There were no symptoms directly referable to the gastrointestinal or genitourinary tract, and the patient's general health had been excellent. Development and growth had been normal.

Examination revealed a well-developed and well-nourished boy who appeared to be in good health. The vital signs were normal, and the blood pressure was 100/58. Examination of the chest revealed no abnormalities. The abdomen was protuberant, with a marked rib flare, widening of the infrasternal angle and prominent, dilated superficial veins. The left side of the abdomen was larger than the right and was occupied by a smooth, cystic mass filling the left flank from the costal margin to the iliac crest and extending to well beyond the midline on the right. The remainder of the physical examination was negative.

Accessory clinical data were within normal limits. The blood showed a red-cell count of 3,870,000 with a hemoglobin of 12.5 gm., and a white-cell count of 8200 with a normal differential. The blood Kahn reaction was negative. Examination of the urine revealed a negative microscopic sediment and culture. The blood nonprotein nitrogen was 32 mg. per 100 cc. The tuberculin reaction was negative.

X-ray studies revealed elevation of the left leaf of the diaphragm and a large soft-tissue mass filling the left side of the abdomen. Gastrointestinal films showed the stomach to be displaced upward and to the right, with small and large intestinal loops pushed into the right half of the abdomen, the descending colon swinging in a curvilinear line over to the right (Fig. 1).

\*Presented at a meeting of the New England Section of the American Urological Association, Boston, April 24, 1941.

From the Department of Surgery, Yale University, and the New Haven Hospital.

†Instructor in urology, Yale University School of Medicine.

‡Clinical professor of urology, Yale University School of Medicine; chief of Urological Service, New Haven Hospital.

Intravenous pyelograms showed normal-appearing internal kidney structures on the right (Fig. 2). On the left,

that the left was not seen to function. The left ureteral catheter met an obstruction approximately 5 cm. above the



FIGURE 1. Gastrointestinal Series, Showing Displacement of the Intestine to the Right Side of Abdomen.

there was a moderate hydronephrosis, with dilatation of all the calyces visualized but with a suggestion of failure



FIGURE 2. Intravenous Pyelogram, Showing Hydronephrosis of the Upper Calyces on the Left and Normal Internal Kidney Structure on the Right.

of filling of the lower portion of the kidney and its calyces. The ureters were not outlined.

Cystoscopy revealed a normal-appearing bladder and trigone. The ureteral orifices appeared normal, except



FIGURE 3. Anteroposterior Film, following Retrograde Pyelography, Showing a Normal Right Ureter and Pelvis and Marked Displacement of the Left Ureter.

ureterovesical junction; the obstruction was passed after slight manipulation, following which the catheter mounted



FIGURE 4. Lateral Film, following Retrograde Pyelography, Showing Displacement of the Left Ureter beneath the Anterior Abdominal Wall.

readily but failed to drain. The pyeloureterogram on the right was normal (Figs. 3 and 4). The left ureter

displaced to the right in the region of the 1st sacral segment, making a sharp bend at the iliac crest. It then



FIGURE 5. *Outline of the Hydronephrotic Lower Left Kidney following the Injection of Sodium Iodide.*

paralleled the right ureter to its upper third, where it crossed to run transversely toward the left renal area.

displaced the ureter medially (Fig. 5); in the lateral view, this structure was seen anteriorly just beneath the abdominal wall.

Review of the intravenous and retrograde studies indi-



FIGURE 7. *X-Ray Film of the Specimen following Injection of Both Ureters with Sodium Iodide.*

cated a massive hydronephrosis in the lower segment of a double kidney, with complete destruction of functioning renal tissue in that pole, associated moderate hydro-



FIGURE 6. *Surgical Specimen.*

lumbar incision, and the cystic mass approached posterolaterally (Figs 6 and 7). Two thousand cubic centimeters of straw colored fluid was aspirated, following which there was sufficient collapse to allow mobilization and removal of the kidney without difficulty. Because of a complex arterial blood supply, heminephrectomy was not done.

The collapsed cystic mass, consisting of an extremely dilated renal pelvis, measured 15 cm in diameter, and contained a small amount of kidney tissue, 4 cm in diameter, at the upper pole. Two ureters were found, one entering the cystic mass below and the other extending upward to enter a separate pelvis at the upper pole. The ureters were separate to a point about 5 cm above the bladder, where they joined. There was no evidence of ureteral dilatation. There was, however, moderate narrowing of the ureteropelvic junction to the lower pelvis. Microscopic study of representative sections showed approximately normal kidney tissue at the upper pole. Sections of the cyst showed thin strips of fibrous tissue in several layers, with intervening dilated calyces lined by a thin layer of epithelium.

Following operation, the patient made an uneventful convalescence and was discharged on the 20th postoperative day. A follow up 4 months later showed him to be in excellent health.

### DISCUSSION

Clinically, cases such as the one presented are significant because of the increased incidence of pathologic change associated with anomalies of the urinary tract. In Mertz's<sup>1</sup> series of 300 cases, 30 per cent were complicated by pathologic change, as compared with 37.5 per cent in Braasch and Scholl's<sup>2</sup> series. The latter authors found both segments most frequently affected by disease; how-

ever, in cases in which only one segment was involved, it was oftener the lower.

Among the pathologic lesions complicating reduplication of the ureter and renal pelvis, in the order of their frequency, are pyelitis and pyelonephritis, nephrolithiasis, ureterolithiasis, hydronephrosis and pyonephrosis due to ureteral obstruction, renal tuberculosis, essential hematuria, nephroptosis, neoplasm and ectopic ureteral implantation.

In reviewing a series of 101 cases of hydronephrosis in infancy and childhood, Kretschmer<sup>3</sup> found the highest incidence in the age group from five to seven years, 28 per cent occurring in this range. Of the various causes of hydronephrosis in this series, 24 per cent were associated with congenital anomalies of the kidney and ureter.

### SUMMARY

An unusual case of massive hydronephrosis in the lower pole of a double kidney, which was due to a congenital ureteropelvic-junction obstruction, with ureteral displacement, is presented. A correct preoperative diagnosis was made, and complete recovery was obtained following nephrectomy.

### REFERENCES

1. Mertz, H. O. Bilateral duplication of the ureters with a compilation of recorded cases. *Urol & Gynec Rev* 24:636-640, 1920.
2. Braasch, W. F. and Scholl, A. J. Jr. Pathological complications with duplication of renal pelvis and ureter (double kidney). *J Urol* 8:507-558, 1922.
3. Kretschmer, H. L. Hydronephrosis in infancy and childhood: clinical data and a report of one hundred and one cases. *Surg Gynec & Obst* 64:634-645, 1937.

## PULMONARY TUBERCULOSIS AND PREGNANCY\*

ROBERT H. BAKER, M.D.,† AND ARTHUR D. WARD, M.D.‡

WORCESTER, MASSACHUSETTS

THE problem of pregnancy associated with tuberculosis has received a good deal of study, and considerable discussion has accumulated in the literature, yet there are few real scientific data of significance concerning it. All that we can hope to do in this paper is to add to the discussion and show how our results compare with those of other institutions.

This problem centers around the fact that pregnancy places an additional strain on a human system that is already devitalized and slowed down by tuberculosis. This added strain cannot but have an adverse effect on the prognosis. On the other hand, the enlargement of the uterus aids in immobilizing the diaphragm and putting the lungs at rest. Yet the marked physical exertion of the second stage of labor again has an adverse effect. In the puerperium, an already debilitated tuberculous patient must combat the effects of pregnancy and labor in addition to those of tuberculosis. It is relatively common to find a flare-up of a previously quiescent or undiagnosed tuberculosis during the puerperium. Accordingly, one must not only treat the tuberculosis itself but also prepare the patient for labor, which is a great strain and a marked physical effort even for a woman in good health; one must plan ahead with the type of collapse therapy best suited to each case, to assure adequate protection to the diseased lung during and following labor. If the patient has already been under treatment by some means of collapse therapy, the problem is somewhat simplified. It is then a question of maintaining the collapse to protect the lung. On the other hand, if the patient is already several months pregnant before the diagnosis is made, the problem of securing an adequate collapse is more difficult, especially when time is limited.

It can be readily seen, then, that each case must be studied individually, from the standpoint of both pregnancy and tuberculosis; this means that there must be co-operation between the obstetrician and the phthisiologist, who must plan together the steps to be taken in preparing the patient for labor. Interruption of the pregnancy by abortion is being advocated less and less,<sup>1-3</sup> because induced

abortion is at times as hazardous as a normal delivery. Abortion, when undertaken, should be performed before the fourth month of pregnancy. Some type of collapse therapy, if not already started, should, if possible, be used.<sup>4, 5</sup> The type of collapse therapy chosen concerns the lung lesion primarily, as well as the pregnancy. The collapse, which does not interfere with the pregnancy, aids in alleviating the symptoms of the tuberculosis—especially cough, which when severe may lead to abortion or premature labor. Seeley, Siddall and Balzer<sup>2</sup> report from the literature a total of 31 cases with thoracoplasty in which the patients went through 34 full-term pregnancies. Collapse therapy is most important during labor. The acute flare-up of the disease following labor is apparently due to the opening up of lesions as the result of a rapid descent of the diaphragm. Artificial pneumothorax can best prevent this effect; if pneumothorax cannot be employed, phrenic crushing will splint the diaphragm and keep it from descending. A case has been reported<sup>6</sup> in which descent of the diaphragm was prevented by artificial pneumoperitoneum induced by admitting 3000 cc. of air into the peritoneal cavity.

In labor, the first stage is entirely involuntary and requires no exertion on the part of the patient. Most of the second stage is voluntary, use of the abdominal muscles being required to expel the fetus. We believe that these patients should be spared the voluntary part of labor. For this reason, it has been the practice of the obstetricians connected with the Belmont Hospital to apply forceps as soon as there is full dilatation of the cervix. Various types of anesthesia have been used, but most of our patients have been delivered under nitrous oxide, oxygen and ether anesthesia. However, the method now employed with these patients is the one that has been found the most satisfactory: local infiltration with perineal block. This is considered safer than spinal anesthesia, and does not incur any of the hazards that may accompany inhalation anesthesia. Local anesthesia has been found to be very satisfactory by both the obstetricians and the patients.

Collins<sup>7</sup> reports that premature labor is no commoner in tuberculous than in nontuberculous patients unless there is an exhausting cough, hemorrhage, fever or marked debility. Other writers<sup>2, 8</sup> find abortion and premature labor slightly more

\*Presented at the annual meeting of the Trudeau Society of Boston, Worcester, May 15, 1941.

†Medical director and thoracic surgeon, Belmont Hospital.

‡Senior physician, Belmont Hospital.

frequent. In our series of cases, 9 out of the 11 infants were full term; the other 2 were one month premature.

A frequent complication,<sup>8</sup> especially in active tuberculous cases, is hemorrhage and shock due to slow involution of the uterus. When it occurs following delivery, it should be combated as promptly and effectively as possible; it can be

facilities of the Worcester City Hospital. The obstetrician who takes care of the patient is on the staff of both hospitals. When a patient goes into labor, she is transferred to the Worcester City Hospital; in uncomplicated cases, she returns to this hospital within twelve to twenty-four hours, and if she has been receiving pneumothorax, air is given on her return, and the collapse is maintained. The



FIGURE 1.

*The photograph on the left represents the x-ray film on entry of a patient who had advanced bilateral pulmonary tuberculosis, with infiltration throughout the entire lung and cavitation below the clavicle on the right and with moderate infiltration on the left, the photograph on the right shows the x-ray film after collapse of the right lung had been maintained for some time.*

guarded against by protection of the patient from long, tedious, exhausting labors and difficult traumatic or operative deliveries.

The babies born to these mothers should, of course, be isolated, particularly if the mother has a positive sputum. The mother should not nurse her child, and provision should be made for its care until it is certain that there is no possibility of communication of the disease.

Eleven cases of pregnancy associated with active pulmonary tuberculosis have been under the observation of the staff of the Belmont Hospital during the last seven years. We still have contact with each of the patients, all of whom are well at present; furthermore, the babies born to these women are living and well. Two patients have survived two pregnancies since they first underwent treatment for tuberculosis. In no case has there been a reactivation of the disease. At this hospital, the facilities for handling obstetric cases are limited. However, we have the use of the

baby remains at Worcester City Hospital until arrangements for its care can be made.

One case in this series was that of a para IV who was admitted to the hospital with the diagnosis of far advanced bilateral pulmonary tuberculosis and with a positive sputum; all the symptoms dated back to the recent pregnancy and confinement. Pneumothorax was given unsuccessfully on both sides. Later, a pneumolysis was performed, and a paraffin pack was applied on the right, followed by extrapleural pneumolysis and a paraffin pack on the left. Still later, a four-stage thoracoplasty and a phrenic crushing on the left were performed. Although this patient was not delivered during treatment for her disease, the case shows that pregnancy can aggravate the condition.

Another case was that of a gravida VI, para IV, who had received treatment for tuberculosis for four years before entry, and who was admitted with a diagnosis of moderately advanced unilateral tuberculosis. Pneumothorax was unsuccessful.



ful, and pneumolysis could not be done. A thoracoplasty succeeded in arresting the disease. The patient again became pregnant three years after the thoracoplasty, but aborted at two or three months; possibly, abortion was induced, although this never could be proved. Nevertheless, there was no flare-up of her disease.

A third case is that of a primipara believed to have moderately advanced unilateral tu-

again delivered by cesarean section. Convalescence was once more uneventful. Following each delivery, there was no flare-up of the disease.

One primipara and 4 multiparas had pneumothorax on one side. One of the multiparas has been delivered twice since treatment was instituted. Four of these 5 cases were classified as moderately advanced, and 3 had a positive sputum; the other was far advanced. Diagnosis was not

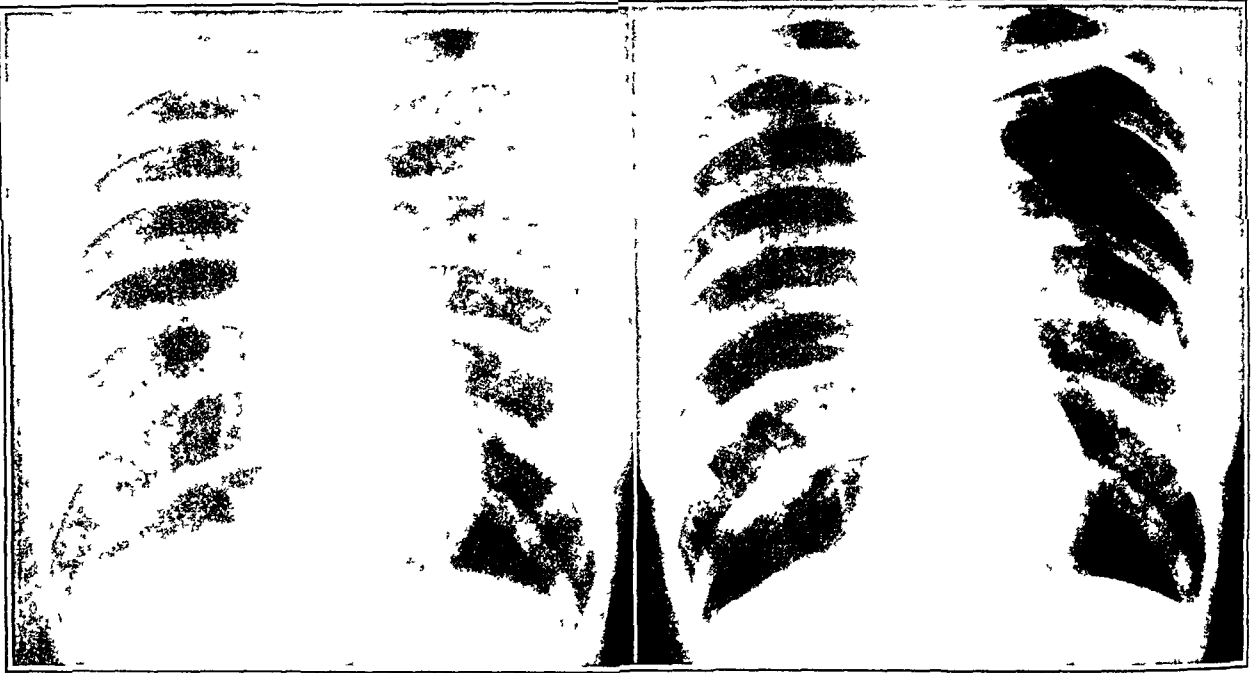


FIGURE 2.

*The photograph on the left shows the x-ray film on entry of a patient who had bilateral pulmonary tuberculosis, with infiltration of the upper half of the lung and cavitation below the clavicle on the left and infiltration of the apex on the right, the photograph on the right represents the x-ray film after bilateral collapse had been maintained for two years.*

berculosis at another hospital, where pneumothorax and pneumolysis were carried out. She was admitted when she was four months pregnant following a threatened miscarriage after she had failed for six months to report to the Outpatient Department for pneumothorax refills. At the time of admission, the lung was practically re-expanded. Obstetric consultants advised that the patient be allowed to continue her pregnancy. She was kept on general supportive treatment until the eighth month of pregnancy, when a phrenic crushing was done. When she came to term, there was considerable overriding of the fetal head because of a generally contracted pelvis, and it was elected to deliver her by cesarean section. Convalescence was uneventful. Eighteen months later, the patient was again admitted, when she was two months pregnant. Two months before term, the phrenic crushing was repeated. One week before term, signs of toxemia appeared, and the patient was

made in 1 case until the third month of pregnancy, and in 2 until the seventh month; pneumothorax was instituted in each case when the diagnosis was made. One patient had had pneumothorax for two years and had maintained a satisfactory collapse; another had had pneumothorax for four years, but at the time of pregnancy, the collapse was unsatisfactory, and two days before delivery a temporary phrenic crushing was done. The patient with far advanced disease was seven months pregnant at the time of admission; she was immediately given pneumothorax on the right, with a good result and relief of symptoms, particularly of a severe cough. All 5 of these patients went through an uneventful labor and puerperium, and 1 of them, who refused to be readmitted, has been delivered again, although not under our care.

Of 3 primiparas with a diagnosis of far advanced bilateral disease and with a positive spu

tum, 1 had been on bilateral pneumothorax for six years, and another for two years; a third, who was five months pregnant when the diagnosis was made, was started immediately on bilateral pneumothorax. All 3 would have had a guarded prognosis even without the added burden of pregnancy. However, in no case was termination of the pregnancy by abortion considered. The patient who had had bilateral pneumothorax for two years refused to come into the hospital when she became pregnant; her collapse was accordingly maintained in the Outpatient Department, and she was not admitted until she went into labor. The patient who had had bilateral collapse for six years was admitted one month before term and had a satisfactory collapse. Both these patients went through a normal delivery and uneventful puerperium. The patient who was five months pregnant at the time the diagnosis was made had a good collapse by the time she reached term and had an uneventful delivery. About one month following delivery, she began to have attacks of pain in the lower right chest and back. Subsequently, the attacks of pain radiated to the epigastric region, and on one occasion were associated with nausea, vomiting and chills. An intravenous pyelogram revealed a ptosis of the right kidney; the lower pole was rotated inward, giving faulty drainage. The ureter was also somewhat tortuous and irregular. The pain was relieved by symptomatic treatment, without recurrence. The patient later had a pneumolysis on the left when some of the adhesions were cut, but because of vascularity the larger adhesions could not be severed. A lysis could not be done on the right because all the adhesions contained large blood vessels. However, the sputum was negative, and the collapse has remained satisfactory.

Each of these patients was given the type of collapse therapy that was best suited to the particular lung lesion. Those who had had an unsatisfactory collapse from pneumothorax were further safeguarded shortly before delivery by a temporary phrenic crushing. The results in each case were satisfactory.

#### SUMMARY AND CONCLUSIONS

The necessity of adequate and proper treatment for the pregnant tuberculous patient is stressed.

If proper treatment is given, a therapeutic abortion because of pulmonary tuberculosis is rarely indicated. Risk of pregnancy in tuberculous women is no greater than that in the nontuberculous if the patients are properly treated. Those who become pregnant should be hospitalized and cared for by obstetricians and tuberculosis specialists.

Collapse therapy, preferably pneumothorax, should be instituted when possible and should never be discontinued during pregnancy. In active pulmonary tuberculosis, it is much more effective than therapeutic abortion.

After labor, treatment for tuberculosis should be carried on vigorously, and no successful collapse therapy should be discontinued without serious study.

#### REFERENCES

1. Thirukuthi S R G. Pregnancy and tuberculosis. *Calcutta M J* 35:22-23 1939
2. Secler W F, Siddall R S and Balzer W J. Pregnancies after thoracoplasty for tuberculosis. *Am J Obst & Gynec* 39:51-56 1940
3. Duime O. De la conservation de la grossesse chez la femme tuberculeuse. *Bulletin méd* 18:45-52 1937
4. Ornstein G G and Epstein I G. Studies on the influence of pregnancy on pulmonary tuberculosis. *Quart Bull Sea View Hosp* 4:420-429 1939
5. Tisdall L H. Pulmonary tuberculosis in an active obstetric service. *Am J Obst & Gynec* 36:472-476 1938
6. Barnes J. Artificial pneumoperitoneum in pulmonary tuberculosis and pregnancy. *Lancet* 2:976 1939
7. Collins C T. Tuberculosis in pregnancy. *Texas State J Med* 35:491-493 1939
8. Strickens H B. Relation of tuberculosis to obstetrics. *Am J Surg* 45:23-35 1940

## MEDICAL PROGRESS

### HETEROGENEOUS RENAL DISORDERS\*

JOHN H. TALBOTT, M.D.†

BOSTON

THIS discussion concerns disorders of renal impairment, functional and anatomic, that are not usually classified as renal disease. Since Bright's disease has been adequately covered in a recent progress report,<sup>1</sup> duplication of any significant portion of that article is avoided. Nor is any of the controversial material on the pathogenesis of arterial hypertension, which has been discussed by White and Smithwick<sup>2</sup> and Weiss,<sup>3</sup> presented. Thus, there is no discussion of the common varieties of acute or chronic nephritis, renal insufficiency in cardiac failure, hypertensive renal disease, congenital polycystic disease of the kidneys, toxemias of pregnancy with renal involvement, pyelonephritis, lipid nephrosis, amyloid kidney, renal stone or renal impairment from prostatic hypertrophy. A word of caution regarding renal impairment in cardiac failure is pertinent. With inadequate blood flow through the kidneys, renal function may be markedly depressed in the absence of marked anatomic changes. The severity of a renal disturbance should be judged only after relief of cardiac failure and restoration of renal blood flow.

#### DIABETES MELLITUS

Two types of renal disorder may develop in patients with diabetes mellitus. During acidosis and coma, the kidneys are subjected to grave insults. A disturbance of the acid-base balance of the blood accompanies ketosis, and is aggravated by the factors that lead to dehydration and shock—inadequate intake of water and salt, vomiting and polyuria. Impairment of ammonia formation ensues, and if the condition is untreated, the ability to excrete ketone bodies reaches a critical stage. Evidence of renal impairment is obvious from the clinical findings of oliguria and anuria and the laboratory findings of albuminuria, cylindruria and nitrogen retention in the blood. Microscopically, the kidneys of patients who have died from diabetic coma show cloudy swelling of the tubular

epithelium and relatively normal glomeruli.<sup>4</sup> The treatment of renal failure is an integral part of the treatment of diabetic acidosis. Restoration of the acid-base balance of the blood follows the judicious use of insulin, glucose, water and salt.<sup>5</sup> The possible development of acute renal failure is a strong argument in favor of constant vigilance toward restoration of water and salt content of the body; this may be neglected during rigorous treatment of the disturbance of carbohydrate metabolism.

The syndrome of diabetes mellitus, hypertension, albuminuria and intercapillary glomerulosclerosis has received considerable attention since its description by Kimmelstiel and Wilson<sup>6</sup> in 1936. Several features identify the syndrome clinically.<sup>7</sup> The incidence is considerably higher in female than in male patients with diabetes. The diabetes mellitus is usually mild, and may appear many years before the onset of hypertension and albuminuria. Sclerosis of the retinal vessels, hemorrhage, exudate and papilledema follow the development of severe hypertension. Albuminuria is usually massive and is presumably responsible for the designation "diabetic nephrosis." Persistent loss of albumin predisposes to edema formation. The albumin-globulin ratio is reversed, and doubly refractile lipid droplets are visible in the urinary sediment by examination with a polarizing microscope. Cardiac failure and nitrogen retention develop terminally. The characteristic pathologic lesion is an interlacing hyalinization of the central portions of the glomerular capillaries. The thickening arises in the intercapillary connective tissue, according to Kimmelstiel and Wilson,<sup>6</sup> whereas Allen,<sup>8</sup> who believes that it arises within the capillary walls, calls it a focal intramural glomerulosclerosis. The glomerular capsule shows deposits of hyaline and lipid material beneath the epithelium. Single glomeruli may be partially or completely hyalinized. The afferent arterioles show fatty and hyaline degeneration, and the efferent arterioles show arteriosclerosis. The lesion is easily distinguishable from the glomerulosclerosis of nephrosclerotic kidneys and from the glomerular hyalinization of glomerulonephritic kidneys observed in nondiabetic persons.<sup>7</sup>

Reprints of articles in this series are not available for distribution, but the articles will be published in book form. The current volume is *Medical Progress: Annual, 1940* (Springfield, Illinois: Charles C Thomas Company, 1941. \$4.00).

\*From the Medical Clinic, Massachusetts General Hospital, and the Fatigue Laboratory, Harvard University. These laboratories are supported, in part, by a grant from the Corn Industries Research Foundation.

†Associate in medicine, Harvard Medical School, and assistant physician, Massachusetts General Hospital.

## DIABETES INSIPIDUS

A dysfunction of the normal economy of the kidneys, rather than renal insufficiency, is a significant part of the pathogenesis of diabetes insipidus. With interruption or failure of consummation of the nervous impulses that normally traverse the supraoptichypophyseal tracts, the pituicytes of the neural hypophysis fail to elaborate a sufficient amount of antidiuretic hormone, and proper proportions of water and salt of the glomerular filtrate are not absorbed by the renal tubules. Polyuria, polydypsia and low urinary specific gravity (usually between 1.001 and 1.005) follow. The increased volume of urine excreted, contrary to casual impression, is not dependent on an increased rate of formation of glomerular filtrate. In fact, when glomerular filtration has been measured in patients with this malady, the value is on the low side of normal and not above normal.<sup>9</sup> The bulk of glomerular filtrate is reabsorbed by difference in osmotic pressure between blood and filtrate, and the antidiuretic hormone provides the stimulus for reabsorption of a smaller amount. The total reabsorption in a normal person is approximately 98 per cent. The excretion into the bladder of the remaining 2 per cent is sufficient to provide for a urine output of at least 2 liters. Reabsorption of glomerular filtrate in diabetes insipidus may be no more than 95 per cent complete. This reduction from the normal is sufficient to increase the daily urinary output to 10 liters. The percentile difference between reabsorption of fluid in a normal person and in a patient with diabetes insipidus, therefore, is not great.

## GOUT

The kidney has been held responsible for the pathogenesis and development of symptoms in patients with gout for several reasons. It is thought by some that a differential inability of the kidneys to excrete uric acid is the primary defect. I do not adhere to this assumption, for reasons presented elsewhere.<sup>10</sup> On the other hand, all students of the disease agree that renal insufficiency is a serious and frequent complication. This is thought to be caused by the burden imposed on the kidneys for the excretion of excessive quantities of uric acid. An increased excretion of uric acid might not be harmful to the kidneys if the solubility were similar to that of other salts, such as sodium chloride and potassium phosphate. The solubility of uric acid is not great, however, and the concentration in serum and glomerular filtrate in gouty patients is near the saturation point. When glomerular filtrate is concentrated in the

convoluted tubules of the kidney, the maximum solubility for uric acid is exceeded and urate salts are precipitated. Persistent precipitation of urate in the tubular lumens eventually leads to renal insufficiency.<sup>10</sup> Patients who develop gouty symptoms in the early decades of life may succumb to renal insufficiency before the age of fifty.<sup>11, 12</sup> Patients who develop symptoms later in life may live a normal span of years. In addition to precipitation of urates in the tubules, urate sludge may appear in the kidney pelvis and may serve as a nidus for urate calculi. The urate stones are friable, and surgical intervention usually is unnecessary should they become lodged temporarily in the ureter.

The subject of renal impairment in gouty patients has been one of great interest to our laboratory. Many of the findings have been published recently in a survey of 22 patients with gout.<sup>13</sup> In this study, the function of the kidneys was investigated by routine clinical procedures,—that is, by ability to concentrate solids, excretion of phenolsulfonphthalein dye, and intravenous pyelography,—as well as by the clearance technics.<sup>14</sup> The patients were selected without regard to extent of disease or duration of symptoms of gouty arthritis. Their ages varied from twenty-eight to eighty-one. With the various procedures used, 18 patients showed some limitation of renal activity. The ability to concentrate solids was observed most frequently. More than two thirds of the group had a depressed inulin and creatinine clearance. Four had severe renal impairment, as shown by an increased concentration of nonprotein nitrogen in the serum. Death ensued in each of these patients in from two to four years after the azotemia was detected. Pathological studies confirmed the clinical findings of renal damage. There was no characteristic renal lesion, however, except for the deposits of sodium urate in the tubules, which were visible grossly and microscopically. Diffuse vascular changes were readily apparent, regardless of age. Evidence of glomerulonephritis and pyelonephritis was also noted. Treatment of the morphologic renal disturbance in gout is supportive rather than specific. An abundant urine volume with an alkaline reaction is desirable. This allays precipitation of urates in the tubular lumens.

## ADRENAL INSUFFICIENCY

Patients with Addison's disease during an adrenal crisis suffer from impending or complete renal shutdown, in addition to the more commonly appreciated metabolic dysfunctions. The ability to excrete phenolsulfonphthalein dye is decreased

markedly, urinary solids cannot be concentrated, and the concentration of nonprotein nitrogen in the serum may be 100 mg. per 100 cc. or greater.<sup>15</sup> More precise tests of renal function, that is, urea and creatinine clearance,<sup>14</sup> may be reduced 50 per cent or more.<sup>16, 17</sup> The mechanism is chiefly from reduction of glomerular filtration and follows hypotension, dehydration, decreased blood volume and hyperproteinemia. During treatment of acute adrenal insufficiency, evidence of severe renal impairment vanishes as the glomeruli resume filtration. Complete restoration of renal function is not achieved, however, and patients with Addison's disease whose symptoms are controlled by treatment with salt and hormones continue to show evidence of renal deterioration. This includes inability to concentrate solids maximally, albuminuria and cylindruria, as well as a depression in clearance of Diodrast and inulin.<sup>18</sup>

Patients with adrenal insufficiency secondary to pituitary hypofunction show similar changes. The impaired inulin and Diodrast clearances may be attributed to vasomotor unresponsiveness, decreased metabolic rate, nonspecific effect of a chronic disease and a lack of specific action by one or more adrenocortical hormones.

#### HYPERPARATHYROIDISM

Parathyroid adenoma or primary hyperparathyroidism is usually complicated by renal disease. The development of the pathologic changes in the kidney is well understood. With an increased concentration of parathormone in the body, serum calcium is increased, and urinary excretion of calcium and phosphate is augmented. Precipitation of calcium phosphate in the urinary tubules and appearance of calcium phosphate casts in the urine follow. The precipitation of calcium salt is enhanced by an alkaline urine. Prolonged deposition of calcium phosphate, with tubular and interstitial damage,—complicated frequently by infection and hydronephrosis,—leads to gross calcinosis in the renal pyramids and renal calculi, and subsequently to clinical renal failure. Albright et al.<sup>19</sup> emphasize the importance of excluding hyperparathyroidism in any patient with renal calculi. Removal of a single parathyroid adenoma or, in a few cases, of two or more diffusely so-called "hyperplastic" glands prevents further deposition of calcium phosphate but does not restore irreparable kidney damage.

Parathyroid hyperplasia secondary to renal disease has been called renal rickets as well as renal dwarfism. The term "rickets" has been applied because the bone changes have been confused

with those seen in infantile rickets. The pathogenesis of renal rickets, however, is dissimilar to that of primary hyperparathyroidism or of infantile rickets. Diffuse hyperplasia of the parathyroid glands follows long-standing renal impairment.<sup>20</sup> The commonest cause of renal disease is a congenital anomaly of the genitourinary tract, although low-grade chronic nephritis, pyelonephritis, nephrosis and polycystic disease have been implicated in some cases. Even though renal damage begins early in life, the characteristic bone changes do not become evident until late childhood or adolescence. The blood pressure is usually normal throughout the disease.

Albuminuria, impaired concentrating ability, reduction of phenolsulfonphthalein excretion and nitrogen and phosphate retention define the amount of renal damage. At least three disturbances may be attributed to phosphate retention: increased output of phosphate in the gastrointestinal tract, impaired absorption of calcium from the gastrointestinal tract and hypocalcemia, and increased parathyroid activity and correction of hypocalcemia. These lead to abnormal bone formation and skeletal changes. At post-mortem examination, the kidneys are small, scarred and contracted—signs of a long-standing process. Histologically, they present diffuse sclerosis, obliteration of the glomeruli, and interstitial and intratubular calcification. Evidence of previous episodes of hypertensive nephrosclerosis is lacking. Attempts at restoration of renal function in renal rickets are fruitless. Considerable benefit to the bony structures can be achieved, however, by a high calcium intake and liberal amounts of a mixture of citric acid and sodium citrate.<sup>21</sup> Absorption of calcium is enhanced, and serum calcium is elevated, so that further stimulus to parathyroid activity is diminished. Normal deposition of calcium in bone is then possible.

Renal rickets with hypercalcemia is a rare syndrome, similar in many respects to typical renal rickets, but a different malady, nevertheless. A complete metabolic study of a patient with this syndrome has been reported from the Massachusetts General Hospital.<sup>22</sup> Renal tubular disease and inability to synthesize ammonia probably represent the underlying lesion. Increased amounts of calcium are excreted in the urine to replace ammonia, which is no longer formed. This leads to calcium depletion in the body, secondary hyperparathyroidism and decreased concentration of serum phosphate. It is therefore a low-phosphorus type of rickets as opposed to the usual high-phosphorus type.

## ALKALOSIS

Temporary impairment of renal function may follow an acute episode of alkalosis, and morphologic deterioration of the kidneys is a complication of prolonged alkalosis. Cyclic vomiting in children and incomplete pyloric obstruction in adults give rise to alkalosis from excessive loss of hydrochloric acid in the gastric secretions. The prolonged ingestion of alkalis produces a similar effect on the hydrogen ion content of body fluids. The inherent danger of renal damage during the Sippy treatment of peptic ulcer was pointed out nearly twenty years ago by Hardt and Rivers.<sup>23</sup> The majority of patients who take soda bicarbonate do not develop clinical symptoms of alkalosis, although some degree of alkalinity of the blood must occur in all.<sup>24</sup> Intolerance for alkalis, rather than excessive ingestion, may be responsible for the development of renal symptoms. Kidneys with a low reserve become inadequate under the load imposed by need for increased excretion of base. Many of the patients who develop renal insufficiency during alkali ingestion are in the age groups that have a high incidence of chronic degenerative disease. It seems advisable to have reliable information regarding renal function in patients with pyloric obstruction and vomiting, as well as in those under consideration for prolonged alkali ingestion, and to appreciate the significance of the development of calcium casts and urinary calculi. Pathological studies of the kidneys of 6 patients who had received large amounts of alkalis during life have been reported by Cooke.<sup>25</sup> The tubules were the site of gross degeneration, lipid changes and calcification, whereas the blood vessels, connective tissue and glomeruli showed little change.

Renal function has been studied by McCance and Widdowson<sup>26</sup> in alkalosis as well as after restoration of the acid-base balance of the blood. Clearances of inulin and creatinine were markedly depressed during alkalosis. Similar observations have been made in our laboratory. It is apparent that acute renal failure, which may develop as a critical episode in alkalosis from decrease in rate of formation of glomerular filtrate, is not necessarily associated with extensive anatomic damage.

## BILATERAL CORTICAL NECROSIS OF THE KIDNEYS

This is a rare condition: less than 100 cases have been reported in the literature. It usually develops in women during or immediately following pregnancy. The child is almost always stillborn. A few cases of cortical necrosis following severe infections, such as dysentery, cholera, diphtheria and pneumonia, have been reported in both sexes. A negative past history for renal disturbance is usu-

ally obtained. Oliguria or anuria may be the first symptom that suggests renal damage. Elevation of the blood pressure, nausea, vomiting, edema and convulsions follow. If any urine is passed, it contains albumin, casts and blood cells. Few recoveries have been reported<sup>27</sup>; in fact, the correctness of the clinical diagnosis may be in doubt if the patient recovers. The kidneys are enlarged at post-mortem examination. The capsules strip easily and reveal a smooth surface, with mottled areas of gray yellow and dark red. The pathologic changes are confined to the cortex; the medulla is normal. Microscopically, the interlobular arteries are occluded, and the area supplied by each artery shows various degrees of necrosis in the tubules, glomeruli and afferent glomerular arterioles.<sup>28</sup> Observers agree that the pathological finding common to most cases is a vascular disease, but agreement is lacking whether endarteritis begins in the glomerular tufts and spreads centrally or whether necrotizing lesions of the interlobular arteries give rise to thrombi with secondary ischemia.<sup>29</sup>

## DISSEMINATED LUPUS ERYTHEMATOSUS

Most patients with disseminated lupus show albuminuria, cylindruria and hematuria before death. These findings by themselves are not vital, since only a small percentage of patients with this malady suffer from renal insufficiency as the primary cause of death. It is significant, however, that once renal damage becomes evident, the prognosis is poor. Patients with this malady have been described who lived for several years without signs of renal damage, but died within a few months after this was evident.<sup>30</sup> A relatively frequent finding microscopically is the "wire-loop" appearance produced by hyaline thickening of the capillary walls.<sup>31</sup> There is also swelling of the glomerulus, cloudy swelling of the glomerular capsule, and irregularity and thickening of the basement membrane. According to Stickney and Keith<sup>30</sup>: "Clinically the duration of renal abnormality is much longer than the pathologic change would indicate: therefore, the disease either is not an ordinary glomerulonephritis or is of low virulence with slow progression. Possibly the changes are secondary to toxic processes and do not represent primary renal disease." The frequent occurrence of bacterial endocarditis, with renal emboli, is also responsible for anatomic changes.

## PERIARTERITIS NODOSA

The primary lesion in this malady is thought to be in the small arteries and arterioles. The vessels in the kidney are involved as part of the generalized disease. Renal findings usually noted

in periarteritis include albuminuria, cylindruria, hyposthenuria and red and white blood cells in the urinary sediment. The association of fever, polymyositis, polyneuritis, eosinophilia and renal disturbance justifies the consideration of this malady in differential diagnosis. Biopsy of a striated muscle is of great help in establishing a correct diagnosis.

### CONGENITAL HEART DISEASE

Patients with advanced symptoms of the tetralogy of Fallot<sup>32</sup> show albuminuria, poor concentration ability, azotemia and impaired pyelographic excretion of Diodrast. Structural changes in the kidneys may be attributed to one or more processes, which include venous congestion, anoxemia, acidosis, glomerular nephritis and subacute bacterial endocarditis with renal infarction. Routine clinical tests of renal function may be negative at earlier stages of the disease. A significant reduction in inulin and creatinine clearance,<sup>14</sup> however, may be demonstrated, as it was in several patients studied at the Massachusetts General Hospital in recent years.<sup>33</sup> This is an excellent example of the fallacy of concluding that the kidneys are normal if clinical tests only are employed.

In patients with coarctation of the aorta, all tests, including inulin clearance, may be negative except Diodrast clearance, which is depressed. The filtration fraction ( $C_r \div C_D$ )<sup>14</sup> may be increased to more than 25 per cent. Friedman and his associates<sup>34</sup> have assumed that reduction in afferent blood flow and renal ischemia is primary and is followed by elevation of blood pressure and efferent arteriolar spasm. Such an interpretation may prove eventually to be inadequate.

### NEPHROTOXIC AGENTS

#### *Hemoglobinuria, Transfusion Reactions and Black-water Fever*

The development of partial or complete suppression of urine following a transfusion is attributed to the agglutination of the donor's cells by the recipient's serum, with subsequent hemolysis and hemoglobinuria. The kidney lesion is primary in the tubules and is similar to that observed in black-water fever.<sup>35</sup> It is caused by precipitation of acid hematin from the glomerular filtrate.<sup>36</sup> As the hydrogen ion concentration of the glomerular filtrate changes from alkaline to acid in the distal convoluted tubules, hematin is precipitated and rapidly plugs the tubular lumens. Pathological examination shows varying degrees of degeneration of the tubular epithelium, and leukocytes, debris and hemoglobin in the lumens. There may be cellular infiltration and edema of the interstitial spaces.

The glomeruli are essentially normal. Opinion is divided concerning whether the pathologic changes result solely from mechanical plugging of the tubules or whether a toxic process is superimposed. Necrosis of the tubular cells and central focal necrosis of the liver argue in favor of a multiple pathogenesis.<sup>37</sup>

There is no specific treatment of anuria following hemoglobinuria. Appreciation of the factors that lead to a transfusion reaction may prevent it in some patients. Discovery of the Rh factor in blood grouping is a vital contribution in prophylaxis. This has recently been discussed by Hooker.<sup>38</sup> The early recognition of a transfusion reaction and cessation of further infusion of whole blood may be lifesaving. An intravenous infusion of an alkaline solution before the tubules have become plugged with acid hematin is theoretically sound, but it is of little benefit after the initial insult. From 100 to 200 cc. of sodium racemic lactate solution given intravenously will keep the tubular urine alkaline for several hours and prevent further precipitation of the degradation products of hemoglobin. Similar alkalization or ingestion of soda bicarbonate by mouth may be useful in the prevention of transfusion anuria in patients who receive several transfusions of apparently compatible blood. Symptomatic treatment of anuria should not be neglected. Maintenance of the normal concentration of the constituents of the blood from day to day should be attempted. Recovery has been reported after anuria of from ten to twelve days' duration and an elevation of the nonprotein nitrogen to 200 mg. per 100 cc. Since the glomeruli suffer only secondarily, renal function may be restored once the tubules become patent. The acid-base balance of the blood should be maintained as effectively as possible until such restoration occurs. Decapsulation of the kidney is discussed below.

#### *Crush Injuries*

A new syndrome, an effect of the total-war principle of World War II, has been described in the British literature by Bywaters and others.<sup>39, 40</sup> It occurs among air-raid casualties who have been buried for several hours under great pressure on one or more extremities. The victim appears to be in fair clinical condition on rescue, and the involved structures show little more than edema and local anesthesia. Thereafter, a series of events rapidly develops that includes impairment of nutrition of the affected limb, signs of progressive renal insufficiency, oliguria, cylindruria, albuminuria and azotemia, circulatory collapse and intractable vomiting. The blood urea may rise to levels of 300 mg. per 100 cc., and the serum

potassium to levels of 7 milliequiv. per liter. Amputation of the affected limb does not stay the lethal processes, and the victim succumbs within a few days or a week. Advanced degenerative changes and brown pigmented casts are seen in the convoluted tubules of the kidney at pathological examination. In place of hemoglobin from the red blood cells, the toxic agent is myohemoglobin,<sup>41</sup> liberated presumably from crushed muscles. This diffuses into the blood stream and is subsequently precipitated in the renal tubules. Janeway<sup>42</sup> has pointed out the desirability of early administration of alkaline fluids as a preventive measure. The problem deserves further study because of its importance in the treatment of civilian and military casualties. Furthermore, it is possible that a syndrome similar to this is an unrecognized industrial hazard following crush injuries in peacetime jobs.

### *Sulfonamide Derivatives*

There is considerable variation among the several sulfonamides regarding the untoward effects on the kidney. Renal complications following the use of sulfanilamide are rare. Sulfathiazole and sulfapyridine are frequent offenders because of the tendency to form crystals in the lumens of the renal tubules. The sulfonamides are handled by the kidney as urea is handled, that is, they are present in the glomerular filtrate in the same concentration in which they exist in the plasma, and are reabsorbed in part by the tubules; the portion not reabsorbed is concentrated and excreted. Precipitation of crystals at the point of concentration in the tubules is unavoidable if adequate fluid is not available for solution. Sulfathiazole crystals appear in the urine more frequently than sulfapyridine crystals,<sup>43</sup> probably because the excretion of the former is more rapid and larger doses are needed for satisfactory blood levels. Plugging of the tubules with crystals may have dire consequences. Hematuria, anuria and retention of nitrogen products are direct effects. Equally alarming is the retention of the acetylated form of the sulfonamides. Since the acetylated forms are much more toxic than the free forms, the situation deteriorates rapidly, and a vicious circle is established. Caution seems indicated, therefore, in the use of sulfonamides in patients with recognized renal impairment. Because sulfonamide calculi are nonopaque to x-rays, this method of examination is not helpful in detecting them. Frequent examination of the blood for the concentration of the free and acetylated forms and examination of the urine for red cells and crystals must be relied on.

Microscopic examination of kidneys damaged by sulfapyridine shows extensive deposits of the acetylated form.<sup>44</sup> There is marked dilatation of the convoluted and collecting tubules and glomerular spaces by precipitated material. The tubules in the cortex appear more uniformly affected than those in the medulla. The prophylaxis and treatment of renal complications following sulfonamide therapy are important. A change of drug must be considered if the concentration of the acetylated form rises in the blood. An increased fluid exchange is helpful in redissolving precipitated material. Alkalinization of urine enhances the solubility of acetylsulfapyridine. The detection of hematuria and crystalluria is a caution signal but is not necessarily a signal for cessation of the sulfonamides.

### *Mercury Bichloride Poisoning*

In acute mercury poisoning, the kidneys bear the principal insult, and many of the serious consequences can be traced to renal impairment. The tubules suffer most, and may be rendered functionless by the accumulation of large quantities of debris.<sup>45</sup> Complete cessation of renal function may persist for a week or longer, with an elevation of nonprotein nitrogen to levels over 200 mg per 100 cc, and as in transfusion anuria, recovery eventually follows. Specific treatment of bichloride poisoning—that is, the administration of sodium formaldehyde sulfoxalate—may be a lifesaving measure in some patients, but the problem of controlling the chief cause of death remains unsolved. Sulfoxalate must be given orally or intravenously within a few minutes after the initial absorption of mercury to be effective. The end product of the reduction of mercuric chloride by sulfoxalate in vitro is about half as toxic as mercuric chloride.<sup>46</sup> The effectiveness of sulfoxalate is enhanced in an alkaline medium, and the use of alkalis is therefore desirable. Other measures that should be instituted at once to prevent additional absorption or reabsorption include lavage of the stomach and rectum and washing of the mouth.<sup>47</sup> Supportive treatment after the initial damage has been done is equally helpful. Unending efforts should be expended toward the treatment of shock and the maintenance of the acid base balance of the blood, before, during and after anuria.<sup>48</sup> This includes the intravenous administration of whole blood, physiologic saline solution and alkaline solutions.<sup>49</sup>

### *Hepatorenal Syndrome*

This designation is introduced with reluctance, since reliable observers have expressed doubt regarding the existence of a syndrome of essential



kidney and liver deterioration. The association of kidney disturbance with jaundice and liver disease is sufficiently common, however, to warrant a discussion, in the absence of general acceptance of a clinical syndrome. The association may be as subtle as the appearance of casts, blood cells and albumin in the urine of patients with surgical jaundice, or it may be as pronounced as in severe eclampsia with advanced renal failure and extensive and irreparable liver damage. An excellent bibliography of the literature prior to 1939 is given in a paper by Wilensky.<sup>50</sup>

There appears to be some confusion in the minds of physicians concerning the statement in textbooks that the liver is the site of formation of urea and that in liver disease a decreased content of urea in the blood may therefore be noted. Bollman, Mann and Magath<sup>51</sup> observed that the conversion of amino acids into urea occurs exclusively in the liver in the dog, and that urea production ceases following total extirpation of this organ. Protein metabolism does not cease, however, and amino acids accumulate in the blood if they are converted into urea. In the clinic, a counterpart of this situation is unique.<sup>52</sup> If only a small amount of functioning liver tissue remains, this is usually sufficient to make some urea, and complete obliteration of functioning liver tissue, with inability to form any urea, is a terminal event of short duration. An increase in concentration of urea in the blood, or no change, is therefore usual in liver disease. In a series of 180 cases of jaundice from medical and surgical causes,—including hepatitis, cirrhosis, and benign and malignant obstruction of the biliary passages,—Meyer, Popper and Steigmann<sup>53</sup> found a moderate increase of nonprotein nitrogen in the blood (40 to 70 mg. per 100 cc.) in nearly 40 per cent, and values greater than 70 mg. in 10 per cent. The mortality rate increased with a rise in the nonprotein-nitrogen level. Furthermore, a change in concentration was of prognostic significance, and an increase of nonprotein nitrogen in conditions amenable to surgery pointed toward the urgent need for surgical intervention.

The pathogenesis of renal insufficiency in liver disease is not yet established. If the hepatorenal syndrome is a clinical fact, kidney deterioration may be an integral process. On the other hand, azotemia may be extrarenal in origin, because of increased breakdown of tissue protein, dehydration and so forth. Whichever may be the correct explanation, azotemia suggests glomerular as well as tubular disturbance. Similar conclusions have been deduced from the study of urea and creatinine clearances<sup>14</sup> in patients with jaundice. These may be reduced from 20 to 75 per cent below nor-

mal.<sup>53, 54</sup> The pathologic picture suggests a degenerative, rather than an inflammatory, process that varies in degree from simple cloudy swelling to extensive necrosis of the tubular epithelium.<sup>55</sup> Glomeruli show proportionately less involvement.<sup>56</sup> Similar pathologic changes have been noted in animals following injection of bile salts (sodium dehydrocholate).<sup>57</sup> A major contribution has been made by Ayer<sup>58</sup> in the study of autopsy material from 18 infants who died of congenital atresia of the bile ducts. A constant microscopic finding in all cases was that of casts containing iron-free, brown pigment. They were present principally in the distal convoluted tubules and the collecting tubules of the cortex. Glomerular lesions were found in only 7 cases; 4 of these showed isolated and partly hyalinized bloodless loops, without epithelial proliferation. The severity of the renal changes was not related to the changes observed in the liver. A similarity between the renal lesions in transfusion reaction, bichloride poisoning and obstructive jaundice was stressed.

### *Decapsulation*

The subject of decapsulation is of interest in a general discussion of nephrotoxic agents, since this form of therapy has been recommended in the treatment of anuria.<sup>59</sup> It is my opinion that nothing is to be gained by decapsulating anuric kidneys. If resumption of urine flow follows decapsulation, restoration would probably have followed conservative treatment. Since decapsulation is an extensive operation and patients with anuria are acutely ill, additional insults may be fatal and are best avoided. Recently, we had an unusual opportunity to study the effects of unilateral decapsulation in a young woman who developed anuria following a transfusion reaction. On the fourth day of anuria, the right kidney was decapsulated, and catheters were placed in both ureters. Resumption of urine flow began about twenty-four hours after operation. There was no difference, however, between the urine volume from the decapsulated kidney and that from the untouched organ. Six weeks later, after normal urine volume had been established for some time and the concentration of nonprotein nitrogen in the blood was almost normal, inulin and Diodrast clearances<sup>14</sup> were done. The ureters were catheterized again so that each kidney could be studied separately. A marked reduction in the rate of formation of glomerular filtrate and in renal blood flow was observed. More significant was the comparison of the two kidneys. No striking difference between the kidneys was noted in any of the functions measured. A

mathematical average of all functions, however, showed a slightly better performance by the untouched kidney in comparison with the decapsulated one. Our results are interpreted as implying that unilateral decapsulation in this patient had no beneficial action on renal function.

#### EFFECT OF POSTURE

##### Orthostatic Hypertension

McCann and Romansky<sup>60</sup> reported clearance studies on 5 patients with hypertension associated with nephroptosis demonstrated by intravenous pyelography. The blood pressures in all patients were elevated when they were erect. Following a period of bed rest of from two to five days, the blood pressures were normal in all except 1 patient. The rate of formation of glomerular filtrate was unaltered by a change in position. On the other hand, the renal blood flow in the erect position was reduced by as much as 50 per cent, with a concomitant increase in filtration fraction. The treatment of only 3 patients is discussed. Two had a nephropexy performed, and 1 was given a ptosis belt. The therapeutic results were not particularly impressive.

##### Orthostatic Albuminuria

The current teaching that orthostatic albuminuria is a thoroughly benign mechanism is probably correct, although strict diagnostic criteria should be applied before acceptance of the diagnosis.<sup>61 62</sup> Two important articles on this subject were written many years ago. Jehle<sup>63</sup> and Sonne<sup>64</sup> observed that orthostatic changes in renal activity occur usually in young, supple persons with a lordosis of the first and the second lumbar vertebra. This was evident from the following observations: when the patient was recumbent in bed, there was neither lordosis nor albuminuria; when the patient was recumbent in bed, with a pillow under the back, albuminuria appeared; standing produced lordosis and albuminuria; standing with the left foot on a stool corrected the lordosis, and the urine became clear. Sonne catheterized the ureters of 6 persons, and in no case was urine from the right ureter abnormal when the patient was erect; however, in 4 cases, the kidney on the left side became anuric, and in the remaining 2, the urine became albuminous. It was thought that the renal vein on the left was probably compressed by the vertebral column, since the vein crosses to the right of the midline. These clinical observations have been confirmed by Chapman<sup>65</sup> and Ryland.<sup>62</sup>

Ryland studied intravenous pyelography by Diodrast, creatinine clearance and urinary constitu-

ents in 5 cases. The excretion of Diodrast and glomerular filtrate was significantly depressed in the erect position in 2, and similar to that in the supine position in 3. All showed casts, red blood cells and tubular epithelial cells in the erect position.

##### March Hemoglobinuria

An excellent review of this subject by Gilligan and Blumgart<sup>66</sup> has appeared recently. This is thought to be a rare condition, but the authors anticipate an increased incidence among men engaged in military activities if the possibilities of its development are appreciated. Hemoglobinuria and hemoglobinemia appear in young healthy men after strenuous marches or runs. In some subjects, lordosis appears to be a factor. The hemoglobinuria is functional in that renal damage cannot be demonstrated. The precise pathogenesis of the disturbance has not been determined, although the similarity of orthostatic albuminuria is apparent. The prognosis is excellent.

#### GASTROINTESTINAL HEMORRHAGE

An increase of nonprotein nitrogen in the blood is a frequent accompaniment of massive bleeding into the intestine.<sup>67</sup> Several processes are responsible. Considerable quantities of hemoglobin remain in the stomach and intestines after severe hemorrhage, which, if assimilated, necessitates the excretion of excessive amounts of urea. The excess urea is cared for promptly, and azotemia is not observed if adequate fluids are available for excretion and if the kidneys are efficient. Usually, this is not realized because of interfering factors, such as shock, hypochloremia, dehydration and starvation, all of which are frequent sequelae of hemorrhage. Furthermore, patients suffering from internal bleeding are apt to be in middle or late life, ages that are accompanied by an increasingly high incidence of degenerative changes of the kidneys. Under conditions of stress, renal insufficiency is not unexpected.<sup>68</sup> Data contrary to this view have recently been presented by Stevens et al,<sup>69</sup> who have concluded that azotemia following blood absorption is unrelated to renal impairment. It is apparent that further investigation is indicated before either conclusion is accepted as final.

#### REFERENCES

1. Fitz R. Kidney disease. *New Eng J Med* 225:109-112, 1941.
2. White J C and Smithwick R H. *The Autonomic Nervous System: Anatomy, Physiology and Practical Application*. 479 pp. New York: Macmillan Co. 1941.
3. Weiss S. Arterial hypertension. *New Eng J Med* 223:939-945, 1940.
4. Tollman J P and Kirk E J. Diabetes mellitus with reference to kidney pathology. *Am J Clin Path* 6:357-370, 1936.
5. Roer H F. Anuria following diabetic coma relieved by hypertonic salt solution. *J Am Med* 101:487, 1934.

- 6 Kimmelstiel, P., and Wilson, C. Inter-capillary lesions in the glomeruli of the kidney. *Am. J. Path.* 12:83 98, 1936
- 7 Newburger, R. A., and Peters, J. P. Inter-capillary glomerulosclerosis a syndrome of diabetes, hypertension and albuminuria. *Arch. Int. Med.* 64:1252-1264, 1939.
- 8 Allen, A. C. So called inter-capillary glomerulosclerosis — a lesion associated with diabetes mellitus morphogenesis and significance. *Arch. Path.* 32:33 51, 1941
- 9 Talbott, J. H. Diabetes insipidus. In *Nelson New Loose Leaf Medicine* Pp 49 54 Vol III New York and London Thomas Nelson and Sons, 1941
- 10 Talbott, J. H. Clinical gout. *Rocky Mountain M J* 38:186 196 1941
- 11 Brogsitter, A. M. *Histopathologie der Gelenk Gicht* 122 pp Leipzig Vogel, 1927
- 12 Schnitzer, M. A., and Richter, A. B. Nephritis in gout. *Am J. M. Sc.* 192:241-252, 1936
- 13 Coombs, F. S., Pecora, L. J., Thorogood, E., Consolazio, W. V., and Talbott, J. H. Renal function in patients with gout. *J. Clin. Investigation* 19:525-535, 1940
- 14 Talbott, J. H. Renal function tests. *New Eng J Med* 226:197 201, 1942
- 15 Rowntree, L. G. Studies in Addison's disease. *J. A. M. A.* 84:327 335, 1925
- 16 Stahl, J., Atchley, D. W., and Loeb, R. F. Observations on adrenal insufficiency. *J. Clin. Investigation* 15:41-46, 1936
- 17 Margitay Becht, A., and Gomori, P. Die Nierenfunktion bei der Addison'schen Krankheit. *Ztschr. f. d. ges. exper. Med.* 104:22 30 1938.
- 18 Talbott, J. H., Pecora, L. J., Melville, R. S., and Consolazio, W. V. Renal function in patients with Addison's disease and in patients with adrenal insufficiency secondary to pituitary pan hypofunction. *J. Clin. Investigation* 21:107 119, 1942
- 19 Albright, F., Baird, P. C., Cope, O., and Bloomberg, E. Studies on the physiology of the parathyroid glands. IV Renal complications of hyperparathyroidism. *Am J. M. Sc.* 187:49 65, 1934
- 20 Albright, F. Renal osteitis fibrosa cystica report of a case with discussion of metabolic aspects. *Tr. A. Am. Physicians* 51:199 212 1936
- 21 Shohl, A. T., and Butler, A. M. Citrates in the treatment of infantile rickets. *New Eng J Med* 220:515 517, 1939
- 22 Albright, F., Consolazio, W. V., Coombs, F. S., Sulkowitch, H. W., and Talbott, J. H. Metabolic studies and therapy in a case of nephrocalcinosis with rickets and dwarfism. *Bull. Johns Hopkins Hosp.* 66:7 33 1940
- 23 Hardt, L. L., and Rivers, A. B. Toxic manifestations following the alkaline treatment of peptic ulcer. *Arch. Int. Med.* 31:171 180, 1923.
- 24 Eisele, C. W. Changes in the acid base balance during alkali treatment for peptic ulcer a clinical analysis of alkalosis in twenty eight patients. *Arch. Int. Med.* 63:1048 1067, 1939
- 25 Cooke, A. M. Calcification of the kidneys in pyloric stenosis. *Quart. J. Med.* 2:539 548, 1933
- 26 McCance, R. A., and Widdowson, E. M. Alkalosis with disordered kidney functions observations on a case. *Lancet* 2:247 249, 1937
- 27 Madding, G. F., Binger, M. W., and Hunt, A. B. Postpartum urinary suppression resembling bilateral cortical necrosis of the kidneys. *J. A. M. A.* 114:1038 1041, 1940
- 28 Talbott, J. H., Gall, E. A., Consolazio, W. V., and Coombs, F. S. Dermatomyositis with scleroderma, calcinosis and renal endarteritis associated with focal cortical necrosis. *Arch. Int. Med.* 63:476 496, 1939
- 29 Penner, A., and Bernheim, A. I. Acute ischemic necrosis of the kidney a clinicopathologic and experimental study. *Arch. Path.* 30:465 480, 1940
- 30 Stickney, J. M., and Keith, N. M. Renal involvement in disseminated lupus erythematosus. *Arch. Int. Med.* 66:643 660, 1940
- 31 Berglund, H., and Medes, G. *The Kidney in Health and Disease.* 754 pp Philadelphia Lea & Febiger, 1935
- 32 Irvine Jones, E. I. M. A clinical study of congenital heart disease in childhood. *Am. Heart J.* 2:121-138, 1926
- 33 Talbott, J. H., Coombs, F. S., Castleman, B., Chamberlain, F. L., Consolazio, W. V., and White, P. D. A record case of the tetralogy of Fallot, with comments on metabolic and pathologic studies. *Am. Heart J.* 22:754 777, 1941
- 34 Friedman, M., Selzer, A., and Rosenblum, H. The renal blood flow in coarctation of the aorta. *J. Clin. Investigation* 20:107 111, 1941.
- 35 Wakeman, A. M., Morrell, C. A., Eisenman, A. J., Sprunt, D. L., and Peters, J. P. The metabolism and treatment of blackwater fever. *Am J Trop Med* 12:407 439, 1932.
- 36 De Gowing, E. L., Warner, E. D., and Randall, W. L. Renal insufficiency from blood transfusion II Anatomic changes in man compared with those in dogs with experimental hemoglobinuria. *Arch. Int. Med.* 61:609 630, 1938
- 37 Goldring, W., and Graef, I. Nephrosis with uremia following transfusion with incompatible blood report of seven cases with three deaths. *Arch. Int. Med.* 58:825 845, 1936.
- 38 Hooker, S. B. Isoimmunization in relation to intragroup hemolytic transfusion reactions. *New Eng J. Med.* 225:871-877, 1941
- 39 Bywaters, E. G. L., and Beall, D. Crush injuries with impairment of renal function. *Brit. M. J.* 1:427-432, 1941
- 40 Beall, D., Bywaters, E. G. L., Belsey, R. H. R., and Miles, J. A. R. A case of crush injury with renal failure. *Brit. M. J.* 1:432-434, 1941
- 41 Bywaters, E. G. L., and Delorey, G. E. Myohemoglobinuria. *Lancet* 1:648, 1941
- 42 Jäneway, C. A. War medicine with special emphasis on the use of blood substitutes. *New Eng. J. Med.* 225:371 381, 1941
- 43 Garvin, C. F. Renal complications due to sulfathiazole. *J. A. M. A.* 116:300, 1941
- 44 Stryker, W. A. The nature of the renal lesion with sulfapyridine therapy. *J. A. M. A.* 114:953, 1940
- 45 MacNider, W. O. B. A study of acute mercuric chloride intoxications in the dog with special reference to the kidney injury. *J. Exper. Med.* 27:519 538, 1918
- 46 Modell, W., Gold, H., Winthrop, G. J., and Foot, E. B. Sodium formaldehyde sulphoxylate in experimental poisoning by mercuric chloride. *J. Pharmacol. & Exper. Therap.* 61:66 81, 1937.
- 47 Rabinowitch, I. M. Unusual findings in a case of acute mercurial poisoning. *Canad. M. A. J.* 39:429 433, 1938
- 48 Peters, J. P., Eisenman, A. J., and Kydd, D. M. Mercury poisoning. *Am J. M. Sc.* 185:149 171, 1933.
- 49 Talbott, J. H., Coombs, F. S., and Consolazio, W. V. Electrolyte balance during recovery from mercury bichloride poisoning. *Arch. Int. Med.* 60:301 311, 1937
- 50 Wilensky, A. O. Occurrence, distribution and pathogenesis of so-called liver death and/or the hepatorenal syndrome. *Arch. Surg.* 38 625 631, 1939
- 51 Bollman, J. L., Mann, F. C., and Magath, T. B. Studies on the physiology of the liver VIII Effect of total removal of the liver on the formation of urea. *Am. J. Physiol.* 69:371-392, 1941.
- 52 Rabinowitch, I. M. Biochemical findings in a rare case of acute yellow atrophy of the liver with particular reference to the origin of urea in the body. *J. Biol. Chem.* 83:333 335, 1929
- 53 Meyer, K. A., Popper, H., and Steigmann, F. Significance of rise of nonprotein nitrogen in medical and surgical jaundice. *J. A. M. A.* 117:847 850, 1941
- 54 Elsom, K. A. Renal function in obstructive jaundice. *Arch. Int. Med.* 60:1028 1033, 1937
- 55 Helwig, F. C., and Schutz, C. B. A liver kidney syndrome clinical, pathological, and experimental studies. *Surg., Gynec. & Obst.* 55 570 580, 1932
- 56 Wilbur, D. L. The renal glomerulus in various forms of nephrosis. *Arch. Path.* 18:157 185 1934.
- 57 Stewart, H. L., and Cantarow, A. Renal lesions following injection of sodium dichlorohalate in animals with and without biliary stasis. *Arch. Path.* 20:866 881, 1935
- 58 Ayer, D. Renal lesions associated with deep jaundice, with comments on their relations to those in the so-called hepatorenal syndrome and in transfusion reactions. *Arch. Path.* 30:26 41, 1940
- 59 Livermore, G. R. The value of nephrostomy and decapsulation in anuria. *J. A. M. A.* 109:1528 1937
- 60 McCann, W. S., and Romansky, M. J. Orthostatic hypertension the effect of nephropoiesis on the renal blood flow. *J. A. M. A.* 115 573-578, 1940
- 61 Thorp, E. G., and Wakefield, F. G. Orthostatic albuminuria a comparison with other types of albuminuria. *Ann. Int. Med.* 6 1565 1578 1933
- 62 Rydand, D. A. The renal lesion in orthostatic albuminuria. *Arch. Int. Med.* 59 848 856, 1937
- 63 Jech, L. Neue Beiträge zur Ätiologie der orthostatischen Albuminurie im Kindesalter. *München med. Wchnschr.* 55:12-14, 1908
- 64 Sonne, C. Beitrag zur Ätiologie der lordotischen (orthostatischen) Albuminurie. *Ztschr. f. klin. Med.* 90:1 6, 1921.
- 65 Chapman, E. M. Personal communication
- 66 Gilligan, D. R., and Blumgart, H. L. March hemoglobinuria studies of the clinical characteristics, blood metabolism and mechanism with observations on three new cases, and review of literature. *Medicine* 20 341 395, 1941
- 67 Meyler, L. Post haemorrhagic uraemia. *Acta med. Scandinav.* 87:313 325, 1935
- 68 Johnson, J. B. The pathogenesis of azotemia in hemorrhage from the upper gastro intestinal tract. *J. Clin. Investigation* 20:161-168 1941
- 69 Stevens, R. J., Schiff, L., Lublin, A., and Garber, E. S. Renal function and the azotemia following hematemesis. *J. Clin. Investigation* 19 733 237, 1940

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTE MORTEM AND POST-MORTEM RECORDS AS USED  
IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

### CASE 28061

#### PRESENTATION OF CASE

A seventy-two-year-old housewife was admitted to the hospital because of pain in the right lower quadrant of the abdomen.

The patient was quite well until the morning of the third day before entry, when she became aware of pain in the middle of her back in the lumbar region. Following lunch, at which she ate less than usual, there was flatulence, but no nausea, vomiting or pain. Some relief was experienced after the patient took "soda" and peppermint in water and lay down. Moderate amounts of gas were passed by mouth and by rectum. The patient slept comfortably that night. The next day, the pain in the back and the abdominal discomfort were replaced by pain in the right lower quadrant of the abdomen. At times, this pain was sharp and stabbing, although without radiation, and at other times it was a mere soreness. Moving about in bed was especially painful; walking was less so. The pain was aggravated by cough and by deep respirations. Bowel movements continued normal, and there were no urinary symptoms, nausea or vomiting. On the day before entry, the pain continued unchanged.

The past history and family histories were not of significance.

On admission, the patient had questionably jaundiced scleras. The heart was within normal size, with sounds of good quality and an apical systolic blow. There were basal "atelectatic" rales in the back, but the lungs were otherwise clear. There was exquisite tenderness and spasticity in the right upper and lower quadrants of the abdomen, with rebound tenderness referred to a point opposite the umbilicus. This point appeared to be the site of maximum tenderness. Peristalsis was active, with sounds of normal pitch.

The temperature was 100°F, the pulse 95, and the respirations 25. The blood pressure was 170 systolic, 70 diastolic.

Examination of the blood showed a white cell count of 18,400 with 82 per cent polymorphonuclears. The urine was normal.

A roentgenogram of the abdomen showed considerable gas in the bowel, without dilatation. The kidney shadows appeared normal, and no stones were seen. The skeleton showed moderate osteoporosis.

An operation was performed immediately after admission.

#### DIFFERENTIAL DIAGNOSIS

DR ALFRED KRANES Before Dr. Hamlin starts his discussion, I may say that there was no question of jaundice in this patient.

DR. EDWARD HAMLIN, JR. May we see the x-ray films?

DR. JAMES R. LINGLEY Here are the loops of small bowel referred to in the record; they were not appreciably dilated. They appeared to be normal in size. Here is one loop, which is probably colon. I think that you can have that much gas in the small bowel just from abdominal pain.

DR. HAMLIN We have, then, an elderly woman with a pathologic process in the abdomen; this apparently progressed to a fairly well localized peritonitis in about twelve hours. The causes that might produce such a story and physical findings are, of course, numerous, and as always, one must first consider acute appendicitis. In an elderly woman, this would be a very good story, and the physical findings do not appear to be inconsistent with a diagnosis of acute appendicitis. The laboratory work all substantiates the diagnosis of peritonitis, or some acute episode in the abdomen, and I cannot exclude appendicitis. It is also possible, although much less probable, that she had acute cholecystitis. I was going to mention the questionable jaundice as possible substantiation of that diagnosis, but Dr. Kranes has ruled it out.

Numerous other processes should be mentioned as possibilities. Twisted ovarian cyst can produce a story and findings similar to these, with spasm masking the mass. Acute diverticulitis, possibly of the cecum, although rare, could produce such a story. However, one part of this history as printed *that seems to me of more significance than anything else* is the fact that the trouble began as pain in the middle of the back in the lumbar region. That should mean that the pain was initiated by a process, either retroperitoneal or in the mesentery, which would also be retroperitoneal. That brings up the possibility of pancreatitis, although this would be an atypical story indeed for pancreatitis, the localization of pain being particularly unusual. But it brings up the question, especially, in this age group, of mesenteric throm

bosis. Mesenteric thrombosis can give a story of this duration. It may be argued that the normal bowel movements and the amount of gas passed by rectum should disturb one, but there is usually no mechanical obstruction of the bowel in mesenteric thrombosis, and if the area to be traversed is not too long, it is quite possible for the bowel contents and gas to pass down through a loop of intestine devoid of peristalsis, much as they would through a hose pipe. It is not unusual to find normal movements in cases of mesenteric thrombosis. It would be interesting to know whether guaiac tests were done on the stools, because at some time or other the patient should have passed blood.

DR. TRACY B. MALLORY: None are recorded.

DR. HAMLIN: It is difficult to determine whether the thrombosis was primarily in the arteries or in the veins. The length of the story, perhaps, is significant in that respect, and I shall make a primary diagnosis of acute venous thrombosis of the small bowel.

DR. LELAND S. MCKITTRICK: Dr. Hamlin has not made it quite clear to me how he has arrived at this very good diagnosis. He may well be right. It is a good diagnosis, but I wonder what makes him think so definitely that this is mesenteric thrombosis instead of the commoner conditions appearing in that region.

DR. HAMLIN: I should say that, to my mind, the main point is the pain in the back, and I tried to bring that out as significant. The location of the point of maximum tenderness, close to the umbilicus, is also of some importance. All the laboratory work and the story seem to be consistent with such a diagnosis, and I am at a loss to think of anything else that would quite fill the bill.

DR. MCKITTRICK: Pain in the back is not an uncommon symptom in strangulation obstruction of the bowel. I have seen one case of infarction of a large ovarian cyst in which pain in the back was the presenting symptom, and I just want to bring that out. It is interesting that Dr. Hamlin has taken pain in the back as the point that has made him think of interference with the mesenteric blood supply.

A PHYSICIAN: The pelvic examination is not mentioned.

DR. CLAUDE E. WELCH: It was entirely negative.

DR. KRANES: I believed that the patient had an acute inflammatory process in the right side of the

abdomen, and that a possible interpretation of the back pain is an acute retrocecal appendicitis. I do not know how often that produces back pain, but a fair number of patients I have seen have had pain either in the flank or somewhat toward the back. Our preoperative diagnosis was acute appendicitis, with probable perforation and abscess formation, because of the exquisite tenderness and what felt like a mass on the right side. The mass was a little higher than one might expect with acute appendicitis. Dr. Welch saw her. He can tell what he thought about the situation.

DR. WELCH: The preoperative diagnosis was retrocecal appendiceal abscess,—although there were points that were not exactly consistent. For one thing, the operation was done at night, and something queer is always bound to turn up at that time. It was possible to palpate a mass under anesthesia. With a right-lower-quadrant (McBurney) incision, it was obvious that the appendix was not the cause. It was retrocecal and freed up easily. On further exploration, it was possible to feel a mass in the central portion of the abdomen. The incision was closed, and a paramedian incision revealed an infarcted twisted piece of omentum, about the size of a fist. In retrospect, this explains the pain in the back to which we had not paid adequate attention. It had a pedicle consisting of two blood vessels and nothing else. It had compressed the transverse colon but had not completely obstructed it. There may have been a good deal of pull on the mesentery of the bowel. The tip of the omentum had become anchored against the ascending colon a short distance above the cecum, and then proceeded on to infarction. The infarcted omentum was removed, and the postoperative course turned out to be uneventful.

#### CLINICAL DIAGNOSIS

Retrocecal appendiceal abscess.

#### DR. HAMLIN'S DIAGNOSIS

Mesenteric venous thrombosis.

#### ANATOMICAL DIAGNOSIS

Infarction of portion of the great omentum.

#### PATHOLOGICAL DISCUSSION

DR. MALLORY: The specimen which reached the laboratory was merely a segment of the great omentum, consisting of hemorrhagic, obviously necrotic, fat tissue.

## CASE 28062

## PRESENTATION OF CASE

A twenty-year-old, single female clerk was admitted to the hospital because of lower abdominal pain of twelve hours' duration.

On the evening before admission, immediately after dinner, the patient developed severe, cramping abdominal pain, radiating from a point immediately above the symphysis pubis to the epigastrium. This pain was fairly continuous, but there were acute, colicky exacerbations. She was nauseated, vomited five or six times, and felt most comfortable lying on her left side, with the thighs flexed.

The patient had been well prior to the acute onset of this illness. Six months before admission, she experienced a similar attack, which was relieved in a few hours by aspirin. The menses were regular, at intervals of thirty to thirty-two days. The last period occurred three and a half weeks before admission. The family history was irrelevant.

On admission, the patient appeared somewhat dehydrated. The tongue was coated. The heart and lungs were normal. There was tenderness in the lower abdomen in the midline and slightly toward the right, most pronounced about 5 cm above the symphysis. There was no spasm, but voluntary contracture was produced by pain. There was no rebound tenderness. The psos sign was negative. On rectal examination, there was marked tenderness in both vaults, more so on the right than on the left. The uterus seemed in normal position, with slight tenderness on movement of the cervix. The vaginal introitus was virginal.

The temperature was 97°F, the pulse 100, and the respirations 20. The blood pressure was 122 systolic, 70 diastolic.

Examination of the blood showed a white cell count of 14,000 with 95 per cent polymorphonuclears. The blood Hinton reaction was negative. The urine showed a + test for albumin.

On the first hospital day, an operation was performed.

## DIFFERENTIAL DIAGNOSIS

Dr S P SARRIS. The problem in this case is essentially the differential diagnosis of an acute condition of the abdomen. Of course, in most cases, practically speaking, the surgeon is primarily interested in distinguishing between the surgical and the nonsurgical abdomen. This decision is made generally, I believe, on the physical signs. When it comes to the individual differential

diagnosis of the various acute intra abdominal conditions, one comes up against a much more difficult problem, since the symptoms and signs are common to so many acute surgical emergencies that only through the variation of minute details and the sequence of the history can one make an accurate differential diagnosis.

On the basis of real peritoneal tenderness, as shown by abdominal examination and confirmed by rectal and pelvic examination, I am going to exclude all medical and nonsurgical conditions. The first diagnosis that I shall consider is, of course, the commonest of the acute intra abdominal surgical emergencies—acute appendicitis. It is true that one can almost never exclude acute appendicitis, however, I shall exclude that first and then continue. One of the reasons it cannot ordinarily be excluded is that appendicitis is so common that even its atypical forms are quite as common as any of the other rare intra abdominal emergencies.

The first specific point for comment is the history of abdominal pain of twelve hours' duration. I believe that the time is important. Most patients with acute appendicitis come in within the second, third or fourth twelve hour period. The fact that this patient came in the first twelve hours suggests that the pain was unusually severe. This point is confirmed later, when it is stated that the patient had severe, crampy abdominal pain. The pain in appendicitis is seldom very severe. It is more an "aggravating" type of pain. The onset, of course, is consistent with appendicitis, but I get the impression that this was a little more sudden than that in the average case of acute appendicitis. The character of the pain is consistent. The number of times that the patient vomited is rather against appendicitis. Usually, adults vomit either not at all or once or twice. This patient vomited five or six times within twelve hours. The previous episode of pain is consistent with appendicitis. Most patients give a history of a previous attack. When it comes to the physical signs I am influenced more by those not in favor of the diagnosis of appendicitis than anything else. The tenderness seems to have been more diffuse than it is with an acute appendix. With a history of twelve hours' duration, that much tenderness by abdominal, pelvic and rectal examinations is more consistent with a perforated appendix, but very few perforate in the first twelve hours. Furthermore, the temperature of 97°F is against the diagnosis of perforated appendix. Consequently, on the basis of the severity of the pain, the suddenness of onset, the frequency of vomiting and the

physical signs, I do not favor a diagnosis of appendicitis.

The next large group to consider is pelvic disorders. Fortunately, in this case, we have a vaginal introitus. The case would be much more difficult if the situation were otherwise, because I should have a hard time excluding salpingitis. As it is, except for the rare blood-borne form of salpingitis, we can quite well exclude that diagnosis. The same argument holds for all conditions that are related to pregnancy. We must consider a ruptured corpus hemorrhagicum; the pain came on suddenly, and the physical signs are consistent with that diagnosis. However, there are two important things against the diagnosis, the chief one being the colicky nature of the pain. In ruptured corpus hemorrhagicum, the onset is acute, but the pain is constant and is more of a soreness from peritoneal irritation than acute pain. Also, the last period occurred three and a half weeks before entry, and a ruptured follicle usually occurs midway between periods.

I think that I can exclude all conditions associated with the upper abdomen. The physical signs and the location of the pain all point to the lower abdomen. Then we have certain conditions, such as acute appendix epiploica and acute Meckel's diverticulum, that I think are practically impossible to diagnose preoperatively. One may suspect them because of certain atypical features, particularly in anyone who has had an appendix removed and has an attack similar to appendicitis. In addition, this patient is too young for diverticulitis.

I might say a word about ulcerative colitis. We have had two cases that began with acute severe, crampy abdominal pain and lower abdominal tenderness without diarrhea. One case we believed to be appendicitis, and the correct diagnosis was made only four or five days after we had ochsnerized the patient for probable ruptured appendix.

Finally, we come down to what we might suspect is the diagnosis in this case, and at this point I should like to ask if any flat abdominal films were taken in this case.

DR. TRACY B. MALLORY: No.

DR. SARRIS: Apparently, those who saw this patient did not consider small-bowel obstruction. If they did, I assume that they would have taken a flat abdominal film. We do not have the common finding in the past history of small-bowel obstruction,—that is, a previous operation,—but 20 to 30 per cent of patients with small-bowel obstruction have not had a previous operation. *There is no statement here concerning the bowels.*

Is there any about whether the patient's bowels had moved since the onset of pain, or about the passage of gas?

DR. MALLORY: I cannot find any.

DR. SARRIS: That would have helped, particularly if there had not been any bowel movement or passage of gas since the onset of the pain. I favor of the diagnosis of small-bowel obstruction are the sudden onset of the pain and its colicky nature. This patient apparently had continuous pain, with what is described as acute colicky exacerbations. There is no mention of the type of peristalsis this patient had—whether it was absent, present or increased. That is one of the most important physical signs of the diagnosis of acute small-bowel obstruction. So-called "obstructive peristalsis" is coincidental with acute exacerbations of crampy pain. The amount of vomiting is also more consistent with that diagnosis than with any other that I have mentioned.

DR. MALLORY: An additional note states that "peristalsis was present, but much diminished."

DR. SARRIS: Of course, I might have to change my diagnosis after that note. I should accept the finding if I were certain of the person who recorded it, because when one looks over the records of small-bowel obstruction, one of the features is the lack of consistency of that sign. One reason is, of course, that the examiner may not be looking for it. However, on second thought diminished peristalsis could be consistent with small-bowel obstruction if circulatory involvement of the obstructed loop had occurred. On still further thought, I shall not let that single finding talk me out of what I think this patient had. The amount of tenderness is consistent with something more than small-bowel obstruction—namely, circulatory interference in the obstructed loop. Tenderness in simple small-bowel obstruction is usually minimal, and if it is present, it is usually localized to the obstructing point.

We can probably exclude the commonest single cause of small-bowel obstruction in a patient not operated on, namely, intussusception, which occurs almost always in infants. The other causes are fairly equally distributed between congenital bands, volvulus, Meckel's diverticulum and foreign bodies, such as gallstones. I think that in this case we can probably exclude gallstones, and that leaves us with congenital bands and a Meckel's diverticulum. Finally, I wish to come back to the question of an acute Meckel's diverticulum, which as I said before falls in a group on which one cannot make an accurate diagnosis preoperatively. Furthermore, I have seen only one case of simple acute diverticulitis. Usually, this disease

is associated with massive gastrointestinal bleeding or small-bowel obstruction. Accordingly, unless this patient had small-bowel obstruction associated with a Meckel's diverticulum, I do not believe that I can make such a diagnosis.

My first diagnosis in this case is acute small-bowel obstruction, with probable, at least early, circulatory interference; my second diagnosis is acute appendicitis. Incidentally, I almost overlooked the possibility of a twisted ovarian cyst, which is, of course, fairly common at this age. However, I exclude it because of the character of the pain, and the fact that the examiners could not feel a mass. If they could feel the vaginal uterus, they should have been able to feel an ovarian cyst.

A PHYSICIAN: Is not the pain just over the symphysis low for small-bowel pain?

DR. SARRIS: I am glad you brought that up. Most textbooks state that the pain in small-bowel obstruction is at or above the umbilicus. In the series of cases that I looked up with Dr. McKittrick, we found one third or more with pain in the lower abdomen.

One other point regarding the diagnosis of acute appendicitis—we are not told that the pain had shifted. If a careful history is taken, one can elicit a shifting pain in acute appendicitis in as high as 85 or 90 per cent of the cases. I do not mean necessarily a shifting from the epigastrium to the right lower quadrant, but a difference in the character of the pain, vague and crampy, followed by tenderness—soreness more than pain. That is absent in this history, unless it was a case of acute appendicitis before localization. I remember one such case we thought had small-bowel obstruction, and while the patient was get-

ting x-rayed, over a period of two or three hours, the pain changed. When he came back to the Emergency Ward, he said that the pain had stopped, and he then could feel soreness on the right side. He had acute appendicitis. It is possible that this patient came in earlier than the average case and before localization.

#### CLINICAL DIAGNOSIS

Acute appendicitis.

#### DR. SARRIS'S DIAGNOSIS

Acute small-bowel obstruction, due to either a congenital band or a Meckel's diverticulum.

#### ANATOMICAL DIAGNOSES

Obstruction of small bowel.  
Congenital adhesive band.  
Gangrene of Meckel's diverticulum.

#### PATHOLOGICAL DISCUSSION

DR. MALLORY: The preoperative diagnosis on the wards was acute appendicitis. At operation, an infarcted piece of intestine, looking like small bowel on first examination was seen and on further exploration turned out to be the end of a Meckel's diverticulum. There was a congenital band, which contained a rather large artery, running across to the base of the Meckel's diverticulum. Behind it, three coils of small bowel had been caught so that there was intestinal obstruction. The Meckel's diverticulum was gangrenous but not perforated.

DR. SARRIS: How about the intestine itself?

DR. MALLORY: That was not infarcted. The appendix was removed and was normal.



# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established in 1828

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND  
PUBLISHED UNDER THE JURISDICTION OF THE COMMITTEE  
ON PUBLICATIONS

Official Organ of  
THE MASSACHUSETTS MEDICAL SOCIETY  
and  
THE NEW HAMPSHIRE MEDICAL SOCIETY

## EDITORIAL BOARD

Joseph Garland, M.D.	Stephen Rushmore, M.D.
William B. Breed, M.D.	Henry R. Viets, M.D.
George R. Minot, M.D.	Robert M. Green, M.D.
Frank H. Lahey, M.D.	Charles C. Lund, M.D.
Shields Warren, M.D.	John F. Fulton, M.D.
George L. Tobey, Jr., M.D.	A. Warren Stearns, M.D.
C. Guy Lane, M.D.	Dwight O'Hara, M.D.
William A. Rogers, M.D.	Chester S. Keefer, M.D.

## ASSOCIATE EDITORS

Thomas H. Lanman, M.D.	Donald Munro, M.D.
Henry Jackson, Jr., M.D.	

Walter P. Bowers, M.D., EDITOR EMERITUS  
Robert N. Nye, M.D., MANAGING EDITOR  
Clara D. Davies, ASSISTANT EDITOR

SUBSCRIPTION TERMS: \$6.00 per year in advance, postage paid, for the United States (medical students, \$3.50 per year); Canada, \$7.04 per year, Boston funds; \$8.52 per year for all foreign countries belonging to the Postal Union.

MATERIAL for early publication should be received not later than noon on Friday.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston, Massachusetts.

## UNITED WAR FUND CAMPAIGN

THE quota of the Physicians' Group for the United War Fund Campaign is \$37,415. To raise this sum, seven hundred and fifty physicians must contribute \$50 each. Obviously, since many are unable to afford such a donation, others are expected to make up the difference.

At the close of the first week of the drive, January 29, approximately 25 per cent of the total quota had been received. This amount represents fair progress toward the realization of the goal, judged by the number of pledges made. However, many have given much more than \$50 per person—indeed, two physicians gave \$1000 each. And the sum pledged seems far less en-

couraging when compared with the donations received in the campaign as a whole: \$3,625,000, nearly 50 per cent of the \$7,600,000 goal.

Thus, it is apparent that only through generosity can the quota of the Physicians' Group be raised. Previous drives have shown that most substantial gifts have been received from those who have budgeted their pledges. Physicians are urged to give their fair share—in periodic payments, if necessary. They will thereby show their response to the patriotic and humanitarian appeal of this drive for victory on the home front and help for those who need it most.

## RECOMMENDATIONS TO MEDICAL STUDENTS AND PHYSICIANS CONCERNING THE NATIONAL EMERGENCY

THE following recommendations to medical students and physicians deserve detailed consideration by all concerned. The efficient utilization of the existing facilities offered by the medical profession and a guarantee of the continued functioning of all sources of medical education are so important in the present national emergency that the procedures advised in this statement by the Procurement and Assignment Service should not be unheeded.

### MEDICAL STUDENTS

All students holding letters of acceptance from the deans for admission to medical colleges as freshmen and sophomores of good academic standing in medical colleges should present letters have letters presented for them by their deans to their local boards of the Selective Service System. This step is necessary in order to be considered for deferment in Class II-A as a medical student. If local boards classify such students in Class I, they should immediately notify their deans and, if necessary, exercise their rights of appeal to the local boards of appeal. If, after exhausting such rights of appeal, further consideration is necessary, request for further appeal may be made to the state director and, if necessary, to the national director of the Selective Service System. These officers have the power to take appeals to the President.

Those junior and senior students who are duly qualified physically for commissions are to be recommended for deferment to local boards by their deans. These students should enroll with the Procurement and Assignment Service for other assignment.

All Junior and senior students in good standing in medical schools, who have not done so, should apply immediately for commission in the Army or the Navy. This commission is in the grade of Second Lieutenant, Medical Administrative Corps, Army of the United States, or Ensign H-V (P), United States Naval Reserve, the choice as to Army or Navy being entirely voluntary. Applications for commission in the Army should be made to the corps-area surgeon of the corps area in which the applicant resides, and applications for commission in the Navy should be made to the commandant of the naval district in which the applicant resides. A medical R O T C student should continue as before, with a view of obtaining a commission as First Lieutenant, Medical Corps, on graduation. Students who hold commissions, while the commissions are in force, come under the jurisdiction of the Army and Navy authorities and are not subject to induction under the Selective Service Act. The Army and Navy authorities will defer calling these officers to active duty until they have completed their medical education and at least twelve months of internship.

#### RECENT GRADUATES

On successful completion of the medical college course, every person holding a commission as Second Lieutenant, Medical Administrative Corps, Army of the United States, should make immediate application to the Adjutant General, United States Army, Washington, D C, for appointment as First Lieutenant, Medical Corps, Army of the United States. Every person holding a commission as Ensign H-V (P), United States Naval Reserve, should make immediate application to the commandant of his naval district for commission as Lieutenant (JG), Medical Corps, United States Naval Reserve. If appointment is desired as Lieutenant (JG), Medical Corps, United States Navy, application should be made to the Bureau of Medicine and Surgery, Navy Department, Washington, D C.

#### TWELVE-MONTH INTERNS

All interns should apply for a commission as First Lieutenant, Medical Corps, Army of the United States, or as Lieutenant (JG), United States Navy or Naval Reserve. On completion of twelve months of internship, except in rare cases in which the necessity of continuation as a member of the staff or as a resident can be defended by the institution, all who are physically fit may be required to enter military service. Those commissioned may then expect to enter military service in their professional capacity as medical officers, those who failed to apply for commission are liable for military service under the Selective Service Act.

#### HOSPITAL-STAFF MEMBERS

Interns with more than twelve months of internship, assistant residents, fellows, residents, junior staff members and staff members under the age of

forty-five, fall within the provisions of the Selective Service Act, which stipulate that all men between the ages of twenty and forty five are liable for military service. All such men holding Army commissions are subject to call at any time, and only temporary deferment is possible, on approval of the application made by the institution to the Adjutant General of the United States Army certifying that the individual is temporarily indispensable. All such men holding Naval Reserve commissions are subject to call at any time at the discretion of the Secretary of the Navy. Temporary deferments may be granted only on approval of applications made to the Surgeon General of the Navy.

All men in this category who do not hold commissions should enroll with the Procurement and Assignment Service. The Procurement and Assignment Service under the executive order of the President is charged with the proper distribution of medical personnel for military, governmental, industrial and civil agencies of the entire country. All those so enrolled whose services have not been established as essential in their present capacities will be certified as available to the Army, Navy or governmental, industrial or civil agencies requiring their services for the duration of the war.

#### PHYSICIANS UNDER FORTY FIVE

All male physicians in this category are liable for military service, and those who do not hold commissions are subject to induction under the Selective Service Act. In order that their service may be utilized in a professional capacity as medical officers, they should be made available for service when needed. Wherever possible, their present positions in civil life should be filled, or provisions made for filling their positions, by physicians over forty five, by physicians under forty-five who are physically disqualified for military service, by women physicians and by instructors and those engaged in research who do not possess an M D degree whose utilization would make available a physician for military service.

Every physician in this age group will be asked to enroll at an early date with the Procurement and Assignment Service. He will be certified for a position commensurate with his professional training and experience as requisitions are placed with the Procurement and Assignment Service by military, governmental, industrial and civil agencies requiring the assistance of those who must be relocated for the duration of the national emergency.

#### PHYSICIANS OVER FORTY-FIVE

All physicians over forty five will be asked to enroll with the Procurement and Assignment Service at an early date. Those who are essential in their present capacities will be retained and those who are available for assignment to military, governmental, industrial and civil agencies may be asked by the Procurement and Assignment Service to serve those agencies.

The maximal age for original appointment in the Army of the United States is fifty-five. The maximal age for original appointment in the Naval Reserve is fifty.

All inquiries concerning the Procurement and Assignment Service should be sent to the Executive Officer, 5654 Social Security Building, 4th Street and Independence Avenue, S.W., Washington, D. C., and not to individual members of the Directing Board or of committees thereof.

### "SPEEDING PRODUCTION OF PHYSICIANS"

UNDER this title, the January 17 issue of the *Journal of the American Medical Association* carries an editorial in which doubt is cast on the wisdom of the shortened schedule adopted by the medical schools of Boston and commented on in the January 29 issue of the *New England Journal of Medicine*. Briefly, the plan provides that the three months heretofore passed in the long summer vacation be eliminated, thus allowing the entrance and the graduation of a class every nine, instead of every twelve, months. After quoting "one leading educator" to the effect that the scheme had not received mature consideration, the editorial goes on to list five difficulties that have arisen. These problems and somewhat different interpretations of them are as follows:

(1) *As an emergency measure, the immediate gain is slight.* The gain may not be great, but it is real and predictable.

(2) *With the elimination of summer vacations, some students will be forced to discontinue their medical education, owing to their inability to earn the necessary funds.* If the Government, particularly in view of its 1942 model of economy, cannot recognize the investment value of a medical student, when physicians are needed so badly, it had better revamp the Selective Service System. Actually, the Government does appreciate the value not only of the medical student but also of the premedical student, and medical schools and colleges could make no better investment than to stake their needy students at a low rate of interest.

(3) *Prescribed R.O.T.C. field training must*

*be discontinued.* If the R.O.T.C. cannot accommodate themselves to anything other than "business as usual," they are overlooking their own interests and responsibilities in the urgency of the moment.

(4) *The technical and teaching staffs must be greatly increased or must devote far more time to their work.* Each medical school must, of course, decide what it is able to do. So far, there has been little, if any, complaint of overwork from the staffs of schools that have adopted the shortened schedule. Furthermore, the medical schools that remain on the old schedule will be a convenience to those college students who cannot complete their premedical requirements until September.

(5) *Unless colleges and hospitals have their curriculums suitably integrated with those of medical schools, the students will lose three to six months waiting for admission as medical students or as interns.* Such a condition has always existed, and there seems to be little necessity of adding another three months each year in the summer.

That professional standards must be lessened is undeniable and inevitable. They have already been lowered by the reduction of internships to one year, and by the renunciation of the somewhat grandiose thought, recently developed, that it takes six or eight years of hospital residence to make a surgeon. To protect the premedical student, it may be necessary to trim medical-school requirements. Physicians with teaching positions will have more work to do, in addition to that already demanded by plans for air-raid protection and civilian defense. Only time can be saved now. Yesterday's leisurely standards must be abandoned. Perhaps the emergency is a little more real and vivid to those who live along the seacoasts than to those in Chicago.

### MEDICAL EPONYM

#### MILROY'S DISEASE

William Forsyth Milroy (b. 1855), professor of clinical medicine and hygiene in the Omaha (Nebraska) Medical College, read a paper entitled "An Undescribed Variety of Hereditary Oedema"

before the Society of the Alumni of Charity Hospital on June 1, 1892; this was published in the *New York Medical Journal* (56: 505-508, 1892). He described the condition as follows

On August 20, 1891, Mr H presented himself for examination for life insurance. The applicant called my attention to his lower extremities. I found a condition of oedema involving the feet and extending up the legs to the knees. Upon inspection the leg presented a slightly rosy hue. Scattered thickly over this base were white spots about the size of a pea. Mr H stated that this oedematous enlargement had existed from birth, that this enlargement of the extremities was a family characteristic which he had inherited from his mother. Fortunately for the purpose of this study, in 1883 a member of the family published a neat volume, giving the family history in America for a period of two hundred and thirty years. The peculiarity now under discussion seems to have entered the family by marriage about 1768. With the aid of this volume and the assistance of members of the family still living, I am able to offer the facts which I present.

1 So far as known, in every case, with two exceptions only, the oedema was present at birth.

2 The location of the oedema has in every case been limited to one or both lower extremities.

3 The presence of the oedema is persistent, never having been known to disappear, temporarily or permanently, except in one instance.

4 It has never been attended by constitutional symptoms, barring the two possible cases in which its first appearance was subsequent to birth.

From these considerations it seems evident that the case under discussion is not one of angio-neurotic oedema. Whether or not the case is one of nervous edema, it is offered that, with others, sufficient material may be accumulated to render possible study of these unusual forms of oedema.

R W B

## MASSACHUSETTS MEDICAL SOCIETY

### COMMITTEE ON MATERNAL WELFARE

#### CAUSES OF MATERNAL DEATH IN MASSACHUSETTS DURING 1940 (continued)

##### RUPTURE OF UTERUS

One case in which autopsy was performed and a diagnosis of ruptured uterus established was an example of very poor obstetrics. An attempt to deliver the patient at home had been made by her physician, and when she arrived in the hospital, her pulse was 130 and she was in shock. The physician had diagnosed a prolapsed arm, and a version had been unsuccessful. A Braxton-Hicks maneuver was performed shortly after entry, and delivery was completed several hours later, with craniotomy of the after coming head.

The rupture of the uterus was not diagnosed; had it been appreciated, laparotomy with probable hysterectomy might well have saved this patient's life.

Another patient with a ruptured uterus died on the table, undelivered. Forceps delivery had been attempted, and version had been tried unsuccessfully before death. Post mortem examination revealed a rupture of the lower segment. Such a death is inexcusable.

Another case of ruptured uterus occurred in association with a partial placenta previa. Version was done, and the patient, while on the table, went into profound collapse and died six hours later. Although no autopsy was performed, this was undoubtedly a case of ruptured uterus.

The next case of ruptured uterus was associated with an abnormal fetus and operative delivery. To deliver the fetus, craniotomy was necessary. During the process, the patient rapidly failed and died one hour after she was delivered. No x-ray film had been taken in this case to determine the size of the fetus, and this death can be attributed only to poor obstetrics.

One case was associated with a long-drawn-out, poorly handled labor. Three ½ ampule doses of pituitary extract were given during labor. The patient died very soon after a difficult forceps delivery. There is no excuse for this death.

In the next case, which was associated with a previous cesarean section, the patient went into spontaneous labor, and the uterus ruptured before she was delivered. Autopsy confirmed the diagnosis.

In the second case with a previous cesarean section, the patient died of a rupture of the uterus during labor. This case was poorly handled throughout.

Another patient, who had had five previous cesarean sections, was in the hospital thirty six hours before operation. Low cervical section was performed, and the patient's condition is said to have been excellent. Six hours later, she went into profound shock and died after four hours. Autopsy showed that the rupture occurred in conjunction with an old scar. The incision of the present operation was intact. This death is hard to explain.

Of these 8 cases,\* 3 were associated with previous cesarean section. This fact emphasizes the seriousness of the initial section, and certainly proves that scars of previous cesarean sections may

\*Further study of the cases of maternal death in 1940 has necessitated a change in the classification of the cause of death in several. Hence the total numbers of cases in many of the groups do not agree with those given in the table in the January 8 issue of the *Journal*. A corrected table will be published in a subsequent issue.

rupture. The last case mentioned, in which an autopsy showed the rupture quite separate from the new incision, is most illuminating as well as very unusual. Those cases of ruptured uterus associated with operating are all examples of very poor obstetrics. These can never be eliminated until obstetrics is more carefully supervised in all obstetric hospitals.

#### ECTOPIC PREGNANCY

Six cases of ectopic pregnancy, 5 tubal and 1 abdominal, resulted fatally.

One patient with tubal pregnancy was operated on five hours after the onset of acute symptoms. Much free blood was found in the abdomen. This patient died of peritonitis, five days after operation.

Another case, which was viewed by the medical examiner and in which no autopsy was performed, was undoubtedly one of exsanguination due to rupture in tubal pregnancy. The patient was not operated on, and the immediate history was not available. She was dead when she reached the hospital.

One patient died during operation. It is quite possible that spinal anesthesia was the primary cause of death, since the operation was begun within a short time of the onset of symptoms, when the patient was said to have been in good condition.

Another patient reached the hospital with a blood pressure of only sixty. This patient died without operation. No transfusion was given.

One patient died, not of the tubal pregnancy but of some pulmonary complication, five weeks subsequently.

There was 1 case of abdominal pregnancy, discovered at autopsy. The diagnosis was entirely missed, and the death was surely avoidable.

#### SURGICAL SHOCK

In 4 cases, the patients died very shortly after cesarean section, and hemorrhage did not seem to be the prime cause of death; hence, they are classified as due to surgical shock. In 1 of these cases, attempts at forceps delivery and version had failed, and in 1 case, a classic cesarean section was performed by a general surgeon. There is nothing to add about the other 2 cases, except that they, too, were badly handled.

One patient was operated on for a retained placenta previa. The history makes little mention of hemorrhage, so that death must be attributed to shock. Autopsy revealed that the uterus was not ruptured, and that a placenta accreta existed. The diagnosis of placenta accreta, of course, should

have been made before death. Had this diagnosis been made, transfusion and hysterectomy might well have prevented this death.

#### SURGICAL DISEASES

*Acute appendicitis.* Three cases of acute appendicitis resulted fatally.

One patient was between five and six months pregnant. The appendix had ruptured before the operation, and the patient died of general peritonitis five days later.

Another patient—about six months pregnant—who was operated on for acute appendicitis aborted eight days after operation. Her condition grew worse, and she died seventeen days after operation.

Another case of acute appendicitis occurred in a patient who was six months pregnant. At operation, the appendix was gangrenous; free pus was found in the abdomen, and the patient died on the fifth day after operation. She aborted spontaneously just before death.

It is very difficult to state that any of these deaths might have been prevented, but if they were under a physician's care from the onset and not diagnosed until after peritonitis developed, the physician certainly should be considered culpable.

*Intestinal obstruction.* One patient was operated on for acute intestinal obstruction, which autopsy proved to be due to adhesions that had followed a gastroenterostomy. This patient was about six months pregnant, and as a last resort, four days before death, delivery was induced. This procedure certainly cannot, in any way, be condoned.

Another patient, who was four and a half months pregnant, died of intestinal obstruction. At operation, it was found that the obstruction was due to adhesions from a previous operation.

One patient, when about seven months pregnant, entered the hospital with a history of having vomited for a few days, with a great deal of abdominal pain. An operation for intestinal obstruction was performed, and at the same time, cesarean section was done. The patient failed, and died of complete intestinal obstruction. If intestinal obstruction demands operation, the uterus should be left alone.

In another case, the patient was about four and a half months pregnant and was under observation at the hospital for five days before the diagnosis of intestinal obstruction was made. This patient aborted shortly before death. Intestinal obstruction was due to adhesions from previous

operations The operation to relieve the obstruction was undertaken too late to be of any value.

It should be axiomatic, in all cases of intestinal obstruction that occur during pregnancy, that the pregnancy be disregarded and that the obstruction be treated; the sooner the operation is performed, the greater the likelihood of recovery. It certainly is a reflection on the medical profession of Massachusetts to allow a patient to remain in the hospital five days before diagnosis and operation, as was true in one of these cases.

## DEATHS

**DOWNEY**—**HUGH J. DOWNEY**, M.D. of Pittsfield died January 31. He was in his sixtieth year.

Born in Adams, Dr. Downey received his degree from Chicago College of Medicine and Surgery in 1912. He was a former secretary and president of the Berkshire District Medical Society. He was a member of the Massachusetts Medical Society and the American Medical Association.

His widow, a son and a daughter survive him.

**POTTER**—**A. CARLETON POTTER**, M.D., of Cambridge, died January 28. He was in his sixty-ninth year.

A native of Cambridge, Dr. Potter received his degree from Harvard Medical School in 1899. At the time of his death he was president of the New England Society of Physical Medicine, and was a fellow of the Massachusetts Medical Society and the American Medical Association.

His widow, a daughter and a sister survive him.

**WEISS**—**SOMMA WEISS**, M.D., of Boston, died January 31. He was in his forty-fourth year.

Born in Hungary, Dr. Weiss received his degree from Cornell University Medical College in 1923. He was assistant at the Thorndike Memorial Laboratory from 1925 to 1929, assistant in medicine at Harvard Medical School from 1926 to 1927, instructor from 1927 to 1929, assistant professor from 1929 to 1932 and associate professor from 1932 to 1939, he was appointed Hersey Professor of the Theory and Practice of Physics in 1939. He was assistant director of the Thorndike Memorial Laboratory from 1930 to 1932, director of the Second and Fourth Medical Services (Harvard) of the Boston City Hospital from 1932 to 1939, and physician in chief of the Fourth Medical Service from 1936 to 1939. He was named physician in chief of the Peter Bent Brigham Hospital in 1938. He was a fellow of the American College of Physicians, the Massachusetts Medical Society and the American Medical Association.

He is survived by his widow and three children.

## WAR ACTIVITIES

### UNITED STATES NAVY

The following medical officers of the United States Naval Reserve have been assigned to active duty in the First Naval District:

Adams, J. F., Lieut. (JG)  
Agnew, J. G., Lieut. Comdr.  
Allman, C. H., Lieut. Comdr.

Alt, R. E., Lieut.  
Apollonio, H. L., Lieut.  
Armitage, H. G., Lieut. Comdr.  
Atkins, H. T., Lieut. (JG)  
Atkinson, G. D., Lieut. Comdr.

Bakst, H. J., Lieut.  
Balch, F. G., Lieut. Comdr.  
Barr, J. S., Lieut. Comdr.  
Benjamin, L. B., Lieut.  
Brown, B. F., Lieut. Comdr.  
Buddington, W. T., Lieut.  
Burrage, W. S., Lieut. Comdr.

Carmody, J. T. B., Lieut.  
Carr, F. B., Lieut. Comdr.  
Carson, P. C., Lieut.  
Cristen, V. G., Lieut. Comdr.  
Chancey, D. J., Lieut.  
Clapp, W. B., Lieut.  
Coffin, W. K., Comdr.  
Cordray, D. P., Lieut.  
Crandon, J. H., Lieut. (JG).

Daniels, D. H., Lieut.  
Davidson, W. B., Lieut. Comdr.  
Dawson, W. E., Lieut. (JG)  
Dement, D. E., Lieut. Comdr.  
Derow, S., Lieut.  
Di Cicco, L. M., Lieut. Comdr.  
Doyle, J. B., Lieut. (JG)  
Drake, E. H., Lieut. Comdr.  
Draper, R. T., Lieut. Comdr.  
Duncombe, A. L., Lieut.

Eley, R. C., Lieut. Comdr.

Faulkner, J. M., Lieut. Comdr.  
Faunce, C. B., Comdr.  
Fay, J. H., Lieut. Comdr.  
Feldman, S. R., Lieut.  
Fleischer, W. E., Lieut. (JG)  
Forbes, A., Lieut. Comdr.  
Freeman, R. G., Lieut. Comdr.

Gardner, S. N., Lieut. Comdr.  
Gibson, S. T., Lieut. (JG)  
Glidden, H. S., Lieut.  
Goehring, H. D., Lieut.  
Golden, S. E., Lieut.  
Goodale, R. H., Lieut. Comdr.

Hamlin, H., Lieut.  
Hanson, F. C., Lieut. Comdr.  
Harris, H. I., Lieut.  
Healy, T. R., Comdr.  
Hendrix, O. C., Lieut. Comdr.  
Houghton, J. D., Lieut.  
Hubbard, J. D., Lieut.  
Hudson, H. W., Lieut. Comdr.  
Hughes, W. N., Lieut. Comdr.  
Hunter, F. T., Lieut. Comdr.  
Hunter, R. W., Lieut. (JG)  
Hynes, E. A., Lieut.

Jacobson, B. M., Lieut.  
Johnson, C. I., Lieut. Comdr.  
Johnson, C. W., Lieut.  
Joplin, R. J., Lieut.

Kennard, H. E., Lieut. Comdr.  
Kunian, D., Lieut.

Lamb, G. R., Lieut.  
Lamphier, J. A., Lieut.  
Lanigan, W. N., Lieut. Comdr.  
Leete, E. D., Lieut. Comdr.  
Lewis, E. I., Lieut.  
Lewis, J. P., Lieut. Comdr.  
Lynch, G. W., Lieut.

Macaluso, A., Lieut. Comdr.  
Macdonald, D. H., Lieut.  
Macdonald, M. E., Lieut. Comdr.  
Mahoney, P. J., Lieut. Comdr.  
Manning, E. P., Lieut. (JG)  
Marshall, J. R., Lieut. Comdr.  
Martin, S. F., Lieut.  
McCann, D. S., Lieut. (JG)  
McCarthy, H. F., Lieut. (JG)  
McCarthy, L. J., Lieut. Comdr.  
McGinn, S., Lieut.  
Merritt, E. L., Lieut. Comdr.  
Miller, R. K., Lieut. Comdr.  
Mintz, E. R., Lieut. Comdr.  
Monks, J. P., Lieut. Comdr.  
Murphy, W. F., Lieut.

Nye, L. S., Lieut. (JG)

O'Brien, T. J., Lieut.  
Ormsby, E. B., Lieut. Comdr.  
Orr, R. B., Lieut. (JG)

Palmer, R. S., Lieut. Comdr.  
Peterson, T. H., Lieut. Comdr.  
Petrone, F. J., Lieut. Comdr.  
Philbrook, F. R., Lieut.  
Pollock, B. H., Lieut.  
Pratt, T. C., Lieut. Comdr.

Regan, J. J., Lieut. Comdr.  
Rooney, J. S., Lieut. Comdr.

Scarcello, N. S., Lieut.  
Schwab, R. S., Lieut.  
Seeyle, E. B., Lieut. (JG)  
Shedden, W. M., Lieut. Comdr.  
Shepardson, R. B., Lieut.  
Smith, E. C., Lieut. Comdr.  
Smith, S. W., Lieut. Comdr.  
Solomon, P., Lieut.  
Sprague, H. B., Lieut. Comdr.  
Stearns, A. W., Comdr.  
Stein, C., Lieut.  
Stoops, W. A., Comdr.  
Stott, A. A., Comdr.  
Swan, C. L., Lieut. Comdr.

Thornton, J. P., Lieut. (JG)

Vance, L. A., Lieut. (JG)  
Vieira, E., Lieut.  
Volk, R., Lieut.

Walker, T. B., Lieut.  
Weiner, F. F., Lieut.  
White, J. C., Lieut. Comdr.  
Wood, H., Lieut. (JG)  
Woodruff, L. M., Lieut. (JG)

Yeomans, A., Lieut.

#### OPPORTUNITY FOR APPOINTMENTS OF PREMEDICAL AND MEDICAL STUDENTS AS ENSIGNS H-V(P), UNITED STATES NAVAL RESERVE

The Secretary of the Navy recently approved a change in Navy regulations whereby it is now possible for those premedical students who have been accepted for entrance to, and all medical students in, Class A medical colleges to be appointed in the United States Naval Reserve in Class H-V(P), provided they meet the physical and other requirements for such appointment.

Students who are acceptable will be given provisional commissions as ensigns, and it is the policy of the Bureau of Medicine and Surgery not to nominate such officers for active duty until after they have completed their prescribed medical studies and shall have served one year's satisfactory internship in a civilian hospital accredited for intern training, or shall have been accepted as acting assistant surgeons in the Navy for intern training.

On graduation, and when the bureau has been informed of this fact by the dean, commissions as Lieutenant (JG) MC-V(G), United States Naval Reserve, will be issued to provisional ensigns and, after serving their internship in non-naval hospitals, they will be nominated for active duty. Application for, or acceptance of, either a provisional or permanent commission in the Naval Reserve, does not preclude the possibility of applying for a commission in the Medical Corps of the Navy. Persons affiliated with the Naval Reserve are not subject to induction into Army service by action of local Selective Service boards.

Navy regulations require that all applications for appointments in the Naval Reserve be filed with the commandant of the naval district in which the applicant resides. The address of the commandant in each district may be obtained from the dean of the medical college.

Application forms may be obtained from the dean's office or from someone designated by him, on request from the Bureau of Medicine and Surgery, Navy Department, Washington, D. C., or from the commandants of naval districts. When an application form has been properly completed, it, together with the other credentials indicated on the application form, should be mailed to the commandant of the naval district. He will issue instructions for obtaining a physical examination, fingerprints and so forth.

A premedical student must enclose with his application for appointment a statement, signed by the dean of a medical college, to the effect that the applicant has been accepted as a first-year medical student in a Class A school for the next entering class.

It is the understanding of the Bureau of Medicine and Surgery that Selective Service boards will accept a statement from the commandant of any naval district, to the effect that an application is on file, as basis for deferment until the application has received final action.

#### REPORT OF MEETING

##### NEW ENGLAND PATHOLOGICAL SOCIETY

The following report of the Executive Committee was presented at a business meeting of the New England Pathological Society on January 13, 1942. The report was accepted, and the recommendations adopted.

\* \* \*

##### RECOMMENDATIONS OF THE EXECUTIVE COMMITTEE CONCERNING THE STATUS OF PATHOLOGISTS DURING THE WAR EMERGENCY

Maximal war effort requires the maintenance of normal standards of health in the civilian population, and an in-

escapable corollary is the continued efficient conduct of civilian hospitals. The inevitable transfer of medical, nursing and technical personnel to military service and of labor to both industry and military service will make this difficult. A more specific danger is the potential loss of certain highly trained specialists, relatively few in number, who are essential to modern hospital practice. Pathologists and roentgenologists are obvious examples. Even in prewar conditions, the supply was inadequate. Many will certainly be required for both the Army and Navy and all hospitals will be left either understaffed or completely desolate unless a skeleton group of reasonable dimensions is maintained in each locality and is so organized that its efforts may be rendered most efficient. In an effort to formulate plans for meeting this prospective emergency, the Executive Committee of the New England Pathological Society proposes the following suggestions for consideration.

At the present moment, only general principles can profitably be outlined. Specific recommendations must await more precise definition of the problem and depend on the number of pathologists drawn into the services and on the number, size and location of the hospitals in need of aid. It is to be noted that the situation differs essentially from that which existed in World War I, since at that time, few of the small or community hospitals had pathological laboratories. It is to be hoped that few hospitals under the pretext of economy will revert to the standards of twenty years ago.

Certain premises can be laid down.

(1) Pathologists must be maintained in the larger metropolitan hospitals and in the departments of pathology of the medical schools, to provide for the accelerated medical curriculum. Administrative officers of schools and of hospitals fortunate enough to maintain a pathological staff should be approached, and their co-operation enlisted in solving the needs of the larger communities.

(2) Although much unessential work is demanded of laboratories in ordinary times that can and should be largely eliminated, an irreducible minimum of diagnostic laboratory procedures exists and must be maintained.

(3) Two methods for maintaining this minimum are available.

(a) To send the material by mail or messenger to central laboratories where pathologists must be maintained, such as the laboratories of the large metropolitan hospitals, the laboratories of the medical schools and the small laboratories where a pathologist is still on service, including private laboratories.

(b) To carry out the technical work locally and arrange a consultative service by which a pathologist will visit at regular intervals to make histologic diagnoses and to supervise and check the technical staff, and by appointment will respond for frozen section diagnoses and autopsies.

Plan (b) service, although obviously preferable, will be much more difficult to maintain. Only a limited number of hospitals can be so provided for, and these must have adequately equipped and staffed laboratories and must be within a limited geographic area in relation to a central laboratory.

In arranging contracts with hospitals, the following principles should be borne in mind.

(1) It should be assumed that all pathologists called to military service are on leave of absence from their respective posts. Therefore, all contracts of consulting pathologists must be terminable with the return of the original pathologist to civilian life.

(2) The hospitals must pay the cost of services rendered. Under Plan (a), this may appropriately be calculated according to the scale of charges authorized by the New England Pathological Society. It is preferable that the fees be paid directly to the pathologist assuming the work and that he, in turn, adjust with his primary employer for the costs of supplies increased technical and secretarial services and so forth. Under Plan (b), the consulting pathologist should receive compensation in the form of a salary proportionate to the work and time involved. The consulting pathologist should not allow the newly assumed duties to cut seriously into the time paid for by his primary employer without negotiating a reasonable adjustment in salary.

(3) The consulting services so offered must fall significantly short of the full service of a pathologist to his hospital. Minimum diagnostic requirements will be met, but the intangible values of constant availability for consultation, for minor administrative tasks and so forth must be sacrificed. It should be possible so to adjust the cost of this limited service that the hospital may, without increased expense, make up to its pathologist in service an approximate difference between his former civilian and his present military salary.

It is proposed that the New England Pathological Society set up a group of regional committees from which any member who expects to enter military service may seek advice concerning his individual problem, and to which hospitals in need of pathological services may apply.

\* \* \*

Subsequent to the meeting, the following regional chairmen were appointed:

*Eastern Massachusetts* Dr Tracy B Mallory  
Massachusetts General Hospital, Boston

*Western Massachusetts* Dr J S Beck  
Memorial Hospital, Worcester

*Maine* Dr Mortimer Warren  
Maine General Hospital, Portland

*New Hampshire and Vermont* Dr Ralph Miller  
Dartmouth Medical School, Hanover, New Hampshire.

*Rhode Island* Dr B Earl Clark  
Rhode Island General Hospital, Providence

*Connecticut* Dr Harry M Zimmerman  
Yale University, School of Medicine, New Haven

## BOOK REVIEWS

*Bacillary and Rickettsial Infections, Acute and Chronic. A textbook—black death to white plague.* By William H Holmes, MD. 8°, cloth, 675 pp. New York: Macmillan Company, 1940. \$6.00.

Before the early part of the nineteenth century at least, no man who undertook the discussion of a particular disease failed to include something of its history. Dr Holmes has resumed that valuable and interesting prac-



tice for each of the maladies with which he deals. Without it, he would still have written an excellent and trustworthy book, for his discussion of etiology, epidemiology, diagnosis, treatment and prevention leaves little to be desired. With it, he has achieved something that for a modern textbook is almost unique. The classic descriptions, of which there are many, are to be cherished. Specifically the maladies considered are plague, tularemia, the rickettsial infections of man, undulant fever, cholera, typhoid and paratyphoid fevers, the bacillary dysenteries, diphtheria, botulism, tetanus, gas gangrene, pertussis, the hemophilic infections, leprosy, tuberculosis, sarcoidosis and the rarer bacillary infections—anthrax, glanders and the like (considered together in a final chapter). The various sections are closed with adequate bibliographies.

One might add that the book is of convenient size and weight and is delightfully printed. It should be a welcome book for anyone whose practice embraces its matters.

*A Research Conference on the Cause and Prevention of Dental Caries.* Chicago, Illinois. July 1 and 2, 1938. Sponsored by The Good Teeth Council for Children, Incorporated. 8°, cloth, 178 pp., with 11 figures, 12 tables, 6 charts and 6 graphs. Chicago: Good Teeth Council for Children, Incorporated, 1940. \$2.00.

In this small volume, reports of research on dental caries by twelve nationally known investigators are assembled, together with discussions by other research workers. The wit and wisdom of Dr. E. V. McCollum, of Johns Hopkins University, who was the moderator of the conference, illuminate the text.

Of the many factors that may be involved in the etiology of dental caries, five are presented in this volume: the morphology of the teeth, the composition of the saliva, the role of vitamin D, age incidence and the flora of the mouth.

The reports and discussions indicate the complexity of the problem of dental caries but bring out quite clearly the directions being taken by these investigators in their search for new knowledge. The anatomic, chemical and bacteriologic background of dental caries is thoroughly discussed.

For those engaged in any phase of research in dental caries, this book should be a valuable reference volume.

*The Endocrine Function of Iodine.* By William T. Salter, M.D. 8°, cloth, 351 pp., with 45 tables and 40 illustrations. Cambridge, Massachusetts: Harvard University Press, 1940. \$3.50.

This is the first of the current series of Harvard University monographs in medicine and public health. The author, now professor of pharmacology at Yale University, has worked with Harington in England on the chemistry of the thyroid gland; with Means and the clinical group at the Massachusetts General Hospital; and at the time of writing, as both clinician and biochemist at the Thorndike Memorial Laboratory of the Boston City Hospital. He is, therefore, well qualified to present a broad view of the subject.

The book does not give a systematic or exhaustive discussion of the thyroid gland, but takes as its point of departure the nature and functions of body iodine, surveying the thyroid and other endocrines only from the standpoint of iodine. This gives in some ways a rather disconnected story; on the other hand, it brings together for the first time all the available studies of iodine in body economy and endocrine balance, and leaves to the textbooks the conventional approach to the thyroid gland and its disease.

The early chapters review the iodine content of all the body tissues and organs, and of the blood and body fluids. The new technics for determining plasma iodine and its fractions have been of great value. There is a discussion of important iodine-containing compounds, such as thyroglobulin, di-iodotyrosine and thyroxine. Then follows a consideration of the role of iodine in thyroid activity, in relation to the pituitary gland and its thyrotropic hormone, and in the interactions of the pituitary and thyroid glands and the gonads. The newer work on iodine balance is presented at some length, and there is a most interesting discussion of radioactive iodine and its recent uses in the study of iodine metabolism by following "tagged atoms" of radioactive isotopes.

Of interest to clinicians is a chapter on clinical problems, in which ten selected cases are cited to show the application of such new diagnostic aids as total-plasma iodine, the "P" and "T" plasma-iodine fractions and the fecal iodine excretion. One is impressed with the need for meticulous control of all conditions in making these tests, and for caution in their interpretation.

There is an appendix for laboratory workers, in which significant new technics are set forth in detail. An exhaustive bibliography adds greatly to the value of the work.

*The Pharmacological Basis of Therapeutics: A textbook of pharmacology, toxicology and therapeutics for physicians and medical students.* By Louis Goodman, M.D., and Alfred Gilman, Ph.D. 4°, cloth, 1383 pp., with 126 illustrations and 67 tables. New York: The Macmillan Company, 1941. \$12.50.

This large volume covers the pharmacology, toxicology and therapeutics of practically all the drugs now in common use. It is an extraordinary compilation—clear, detailed, accurate, well documented, adequately illustrated and superbly indexed. No book in recent years has so appealed to the reviewer as a fundamental contribution, finely executed. Although the price is not low, the book is well worth its cost. It should be in every medical library and research center, and would be a valuable addition to many physicians in their private libraries. The book will constantly be referred to by any doctor who attempts to keep up with modern trends, and its value to the scientific investigator is great.

The volume is excellently published; the paper is light, but adequate, the illustrations are clear, and the bibliography is easy to read.

*A Textbook of Dietetics.* By L. S. P. Davidson, B.A. (Cantab.), M.D. (Edin.), F.R.C.P. (Edin. and Lond.), F.R.S.E. and Ian A. Anderson, M.B., Ch.B. (Aberd.). With diet sheets constructed by Miss Mary E. Thomson, S.R.N., and a foreword by Sir John Boyd Orr, M.D., D.Sc., LL.D., F.R.S. 8°, cloth, 324 pp., with 27 tables. New York: Paul B. Hoeber, Incorporated, 1941. \$4.25.

The problem of nourishment in some form or other has always occupied the attention of man. This has now become a mass problem because of widespread economic and social dislocations. The introduction of more commercial methods of food preparation is also a source of abnormal nutrition. It is incumbent on every physician to be conversant with a knowledge of dietetics, which is applicable to the recognition of late and frank cases of vitamin deficiencies, problems of malnutrition and obesity and the care of specific metabolic diseases. This book can be regarded as an adequate introduction to the subject. Unfortunately, since it is a British publication, many preparations are mentioned that are unfamiliar to Americans, and the difference in dietary habits is noteworthy. Both considerations lessen the value of the book for Americans.

# The New England Journal of Medicine

Copyright 1947 by the Massachusetts Medical Society

VOLUME 226

FEBRUARY 12, 1942

NUMBER 7

## THE DIAGNOSIS OF CORONARY-ARTERY DISEASE\*

H M MARVIN, MD†

NEW HAVEN, CONNECTICUT

IT IS surely unnecessary to remind an audience composed of physicians that the many factors that may enter into the diagnosis of coronary artery disease cannot possibly be discussed in any adequate or comprehensive fashion in the space of a few minutes, or indeed of a few hours. I am sure that I shall be forgiven if I attempt to present in abbreviated and almost tabular form a few of the more important established facts relating to this condition. Any appearance of dogmatism or unjustified authority in my statements is due solely to limitations of time, which do not permit the discussion of controversial points or the presentation of opposing evidence.

The term "coronary-artery disease" so widely used today includes all known varieties of change in these vessels, and some of them are so infrequent or of such slight clinical interest as to justify their exclusion. In general, ability to recognize disease of the coronary arteries is restricted to conditions that interfere with the nutrition of the myocardium sufficiently to cause symptoms, changes in the x-ray film or alterations in the electrocardiogram. Changes of this degree are usually due to arteriosclerosis, with narrowing or closure of coronary branches, and I interpret the term "coronary-artery disease" to mean coronary arteriosclerosis for the purposes of this discussion. And the question that I shall attempt to answer, in part, is, What criteria will enable one to suspect, or to recognize with certainty, structural changes in the coronary arteries that interfere with the heart's nutrition sufficiently to be of consequence to the patient?

### Clinical Evidence

There is now complete agreement among authorities that the presence of typical and unmistakable anginal pain should be regarded as evidence that the coronary blood flow is inadequate for the needs of the heart muscle, and that this inadequacy is due in most cases to arteriosclerotic narrowing or closure of the vessels, although typical anginal pain may occur in the presence of normal coronary arteries in cases of severe anemia or during prolonged paroxysms of tachycardia with excessive ventricular rates. It may also occur in the absence of coronary arteriosclerosis in occasional cases of hyperthyroidism, or in patients whose hearts are greatly enlarged as a result of hypertension or rheumatic disease of the aortic valves, presumably because the increased demands of the hypertrophied myocardium for blood are not met by a corresponding increase in the coronary blood flow.

The question that immediately arises is, What is typical and unmistakable angina? Most cardiologists frequently encounter patients whose physicians have assured them that they have angina pectoris, when a careful analysis of their symptoms reveals that they do not. The diagnosis of angina is based, with one possible exception, exclusively on the history given by the patient, and not in any degree on the physical or x-ray examination, or the electrocardiogram. And the history that compels a diagnosis of angina includes among its more significant features the following: the discomfort in the chest is dull, squeezing or constricting, never sharp or knifelike, it occurs usually beneath the sternum, and not over the body of the heart; if it radiates, it is almost always to the shoulder and down the inner aspect of the arm, more frequently the left; the discomfort is of brief duration, usually from half a minute to three or four minutes; it is constant from the moment of onset until its complete disappearance—that is, it does not come and go, or wax and wane in intensity, for periods of seconds; it has a close rela-

\*Presented at the New England Postgraduate Assembly, Cambridge, Massachusetts, October 30, 1941.

†Associate clinical professor of medicine, Yale University School of Medicine, and attending physician, New Haven Hospital.

the T wave may disappear if the curve is recorded during deep inspiration or while the subject stands erect. Both the deep Q and the inverted T waves may remain for many years without change and without the appearance of any signs of heart disease. I have little hesitation, therefore, in expressing the opinion that it is unjustifiable and even deplorable to interpret a deep Q wave in Lead 3 by itself as an indication of heart disease, and especially as a specific sign of coronary sclerosis.

And, finally, I come to that portion of the curve that has caused greater trouble than all others combined: the ST segment and T wave. I cannot discuss this in the detail that it merits. Depression or elevation of the ST junction or segment and inversion of the T wave are apparently more generally accepted than any other changes in the electrocardiogram as indications of heart disease, and especially of coronary arteriosclerosis. Whether or not this statement is justified can be judged by the following quotation from a recent article by Sprague<sup>5</sup>:

Without the hope of its being complete, the following list of conditions, other than coronary atherosclerosis, responsible for abnormalities of S-T and T segments is submitted:

- |                         |                          |
|-------------------------|--------------------------|
| 1. Drugs                | i. Avitaminosis,         |
| a. Digitalis            | especially beri-         |
| b. Quinidine            | beri                     |
| c. Tobacco              | j. Acidosis              |
| 2. Myocardial infection | k. Alkalosis             |
| a. Rheumatism           | l. Anoxemia              |
| b. Diphtheria           | m. Shock                 |
| c. Trichinosis          | 6. Changes in posture of |
| 3. Other general infec- | the patient              |
| tions                   | 7. Axis deviation        |
| a. Pneumonia            | 8. Abnormal heart        |
| 4. Pericarditis         | rhythms                  |
| 5. Toxemia and          | a. Paroxysmal tachy-     |
| metabolic               | cardia and               |
| disorders               | auricular                |
| a. Uremia               | fibrillation             |
| b. Diabetic acidosis    | b. Sinus tachycardia     |
| c. Hypocalcemia         | 9. Alterations in vago-  |
| d. Hyperthyroidism      | sympathetic              |
| e. Hypothyroidism       | tone                     |
| f. Insulin shock        | a. Pain                  |
| g. Addison's disease    | b. Fear                  |
| h. Anemia               | c. Anesthesia            |

- |                        |                       |
|------------------------|-----------------------|
| 10. Pulmonary embolism | f. Syphilis of aorta  |
| 11. Miscellaneous      | g. Gall bladder dis-  |
| a. Periarthritis       | case                  |
| nodosa                 | h. Scleroderma        |
| b. Trauma              | i. General anasarca   |
| c. Malignancy of       | j. Cooling the heart  |
| myocardium             | through inges-        |
| d. Dissecting aneu-    | tion of ice water     |
| rysm of corona-        | k. Terminal states of |
| ry artery              | all kinds             |
| e. Dissecting aneu-    | l. Unexplained        |
| rysm of aorta          |                       |

This list contains forty-one different conditions, thirty-three of which do not imply heart disease!

I do not wish to imply that coronary atherosclerosis does not cause changes in the ST segments and T waves, because undoubtedly it does. But I do wish to state emphatically that coronary disease is only one of many factors that cause such changes, and it is impossible to decide from the electrocardiogram alone which of these many causes is responsible. One might just as well attempt to make a correct and specific diagnosis of disease on the sole basis of slight leukocytosis, without any knowledge of the clinical picture and other laboratory tests.

I think that this whole matter may be summarized in one sentence. If myocardial infarction is excluded, *there is no change in the electrocardiogram that in itself justifies the diagnosis of coronary disease*, because the alterations on which this diagnosis is based may be—and often are—due to other causes. I am in the heartiest agreement with Wilson<sup>6</sup> when he says, "It would be better if this term [coronary disease] were never used under any circumstances in connection with the interpretation of the electrocardiogram."

303 Whitney Avenue

## REFERENCES

- Blumgart, H. L., Schlesinger, M. J., and Davis, D. Studies on the relation of the clinical manifestations of angina pectoris, coronary thrombosis, and myocardial infarction to the pathologic findings, with particular reference to the significance of collateral circulation. *Am. Heart J.* 19:1-91, 1940.
- Master, A. M., Gubner, R., Dack, S., and Jaffe, H. L. The diagnosis of coronary occlusion and myocardial infarction by fluoroscopic examination. *Am. Heart J.* 20:475-485, 1940.
- Barritt, A. S., Jr. The clinical significance of electrocardiographic low voltage QRS groups in the presence of normal T waves. *Brooklyn Hosp. J.* 2:147-149, 1940.
- Leach, C. E., Reed, W. C., and White, P. D. Low voltage of the QRS waves in the electrocardiogram, with especial reference to Lead IV. *Am. Heart J.* 21:551-563, 1941.
- Sprague, H. B. Normal electrocardiograms in the presence of coronary disease. *Mod. Concepts Cardiovasc. Dis.* 10 (No. 10), 1941.
- Wilson, F. N. Review of Graybiel and White's *Electrocardiography in Practice* (Philadelphia: W. B. Saunders and Company, 1941). *Am. Heart J.* 21:830, 1941.



just described, a condition of simple vaginal hydrocele (ordinary hydrocele) exists. This is shown in Figure 2A by a diagram similar to those of Jacobson<sup>18</sup> and Campbell.<sup>24</sup> If the distal portion of the stalk of the processus vaginalis fails to be-

the processus vaginalis becomes obliterated for only a very short distance at the level of the internal inguinal ring, and if a large amount of hydrocele fluid accumulates, further stretching of the sac toward the abdomen can occur, producing

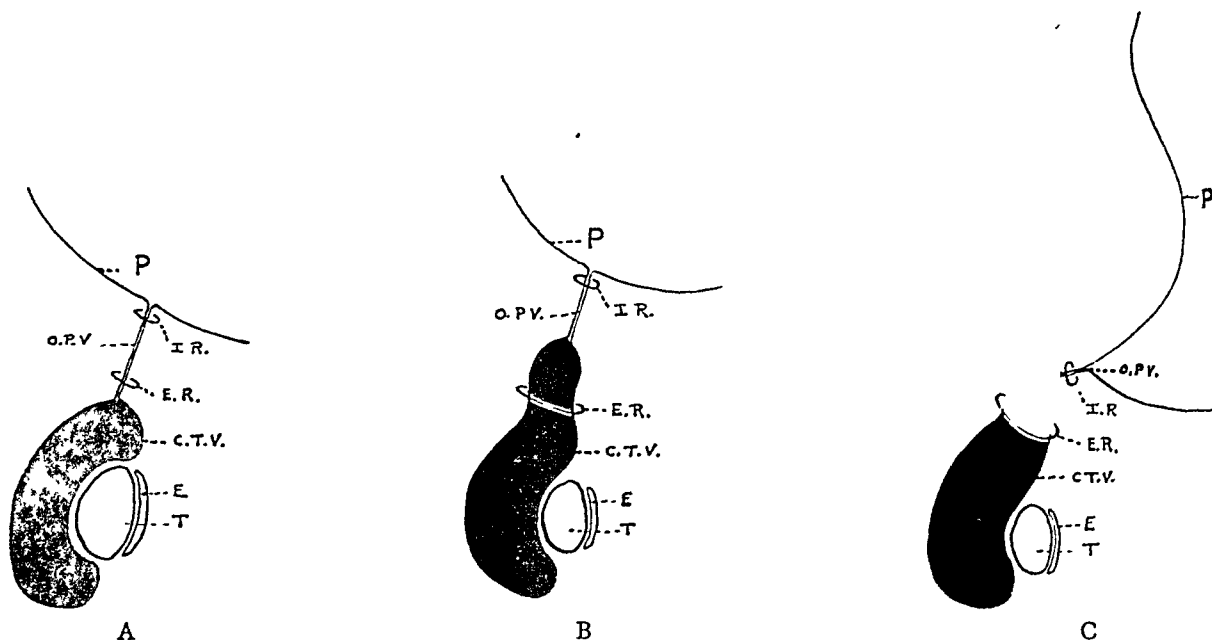


FIGURE 2. *Diagrams of Several Types of Hydrocele.*

A.—*Simple or vaginal hydrocele*; B.—*infantile hydrocele*, C.—*abdominoscrotal hydrocele*. Abbreviations: P.—*peritoneum*; E.—*epididymis*; T.—*testis*; I.R.—*internal inguinal ring*; E.R.—*external inguinal ring*; O.P.V.—*obliterated processus vaginalis*; C.T.V.—*cavity tunica vaginalis*.

come obliterated, so that the cavity of the tunica vaginalis extends upward to the level of the inguinal canal instead of to a point just above the

the condition known as abdominoscrotal hydrocele (Fig. 2C).

Several different theories have been held regarding the development of abdominoscrotal hydrocele and its relation to the peritoneum. Dupuytren<sup>1</sup> believed that with extreme distention the ordinary vaginal hydrocele could push its way up through the inguinal canal and assume an abdominal position. Kocher<sup>14, 15</sup> shared this view. Against the views of Dupuytren and Kocher may be cited the numerous cases of ordinary hydrocele in which the fluid is confined under considerable pressure, without extension beyond the confines of the simple vaginal hydrocele. Probably, the more logical explanation—expressed by Jacobson,<sup>18</sup> Macewen<sup>25</sup> and Tanzer,<sup>26</sup> with whom I agree—is that a persistent type of high infantile hydrocele exists in which the processus vaginalis is obliterated only at the level of the internal ring. If distention of the upper portion of the sac occurs, there are no confining structures on the posterior or peritoneal aspect to limit the abdominal expansion. As Tanzer has stated, the abdominal sac can be considered an evagination from the proximal end of the hydrocele sac (Fig. 2C).

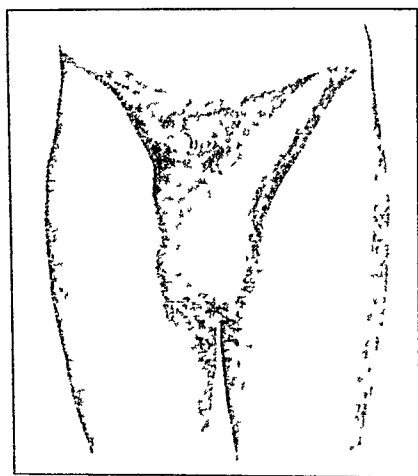


FIGURE 3. *Drawing of the Infantile Type of Hydrocele (Bazy<sup>16</sup>).*

testis, and if that cavity becomes filled with fluid, there exists, as originally outlined by Jacobson, an infantile type of hydrocele (Figs. 2B and 3). If

The relation of the sac to the peritoneum and the abdominal wall deserves discussion. From the case reports, it becomes obvious that several types of abdominoscrotal hydrocele exist. In fact, Delbet,<sup>27</sup> in 1896, proposed that they be divided into properitoneal, interstitial and superficial types, on

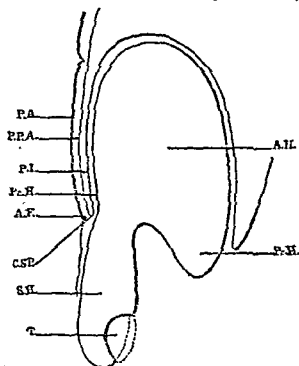


FIGURE 4. Diagram of Layers of the Abdominal Wall and Peritoneum and Their Relation to an Abdominal Hydrocele (Bazy<sup>16</sup>).

Abbreviations: P.A.—abdominal wall; P.P.A.—peritoneum covering abdominal wall; P.I.—peritoneum covering iliac fossa, compressed by tumor; Pa.H.—wall of hydrocele; S.H.—scrotal portion of hydrocele; A.H.—abdominal portion of hydrocele; P.H.—pelvic portion of hydrocele; A.F.—femoral arch; C.S.P.—peritoneal cul-de-sac; T.—testicle.

the basis of the relation to the abdominal wall. To make this classification complete, one should add the retroperitoneal type. Bazy believed that there were two layers of peritoneum between the abdominal wall and the hydrocele sac (Fig. 4) and Lister,<sup>8</sup> after a post-mortem dissection on a case, declared that "it formed a tumor beneath the peritoneum lying in the iliac fossa and the lower part of the anterior wall of the abdomen." Coleman<sup>28</sup> also considered his case to be of the retroperitoneal type. On the other hand, Delbet believed that his case was of the superficial type, the sac lying superficial to the muscles of the abdominal wall. The majority of cases are, I believe, of the properitoneal type, in which the abdominal portion of the sac lies between the muscles of the abdominal wall and the peritoneum (Fig. 5).

The clinical aspects of abdominoscrotal hydrocele are of interest since the occurrence is relatively uncommon, and most communications on the subject consist of single case reports.<sup>29-40</sup> Some of the present-day texts on urology fail to mention the condition, although others<sup>41, 42</sup> briefly describe it. If Brandenburg<sup>43</sup> is correct in estimating the cases collected up to 1921, there have now been about 53 reported cases (including the one described in this paper)

The majority of patients were in the second or third decade of life when they sought treatment, although Kocher reported cases in children one and thirteen years old, and Syme<sup>44</sup> reported a case in a four-year-old child. The oldest men described in the case reports were the fifty-four-year-old patient of Fuchs<sup>9</sup> and the fifty-five-year-old patient of Wettergren.<sup>45</sup>

Both right and left scrotal regions have been affected and with approximately equal frequency. The history is usually that of a painless swelling developing first in the scrotal region and later extending to the groin and abdomen. Many patients are apparently not inconvenienced by the large abdominal protrusion that develops, although Steele's<sup>10</sup> patient complained of difficulty in walking. However, the symptoms in Steele's case may have been due to the pressure on an undescended testis rather than to the abdominal swelling per se.

Physical examination discloses not only the scrotal swelling but an abdominal tumor that can

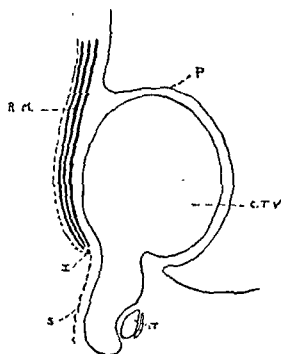


FIGURE 5. Diagram of the Relation of the Peritoneum and Abdominal Muscles to an Abdominoscrotal Hydrocele.

Abbreviations: A.M.—abdominal muscles; P.—peritoneum; C.T.V.—cavity of tunica vaginalis; I.—level of inguinal ligament; S.—scrotal wall; T.—testis and epididymis.

reach large proportions. It is not unusual to find the abdominal protrusion, the size of a six or seven months' gravid uterus, extending above the level of the umbilicus and beyond the midline. The tumor is smooth, firm, nontender and flat to percussion. The scrotal tumor transilluminates well unless the sac contains blood. Pressure on the abdominal portion of the sac creates a fluid wave or thrill to the scrotal area. Usually, coughing creates a definite impulse in the scrotal region, a phenomenon similar to the fluid wave produced by sudden compression of the abdominal portion of the sac. Occasionally, the abdominal swelling is extensive enough to give the impression of ascites. Catheterization of the bladder obviously fails

to reduce the size of the tumor. In the pelvic type of abdominoscrotal hydrocele, rectal examination should disclose a ballotable pelvic mass continuous with the scrotal swelling. Holmes<sup>21</sup> injected 60 cc. (2 ounces) of saturated sodium iodide into the scrotal sac before operating, and obtained a graphic picture of the large abdominoscrotal sac. It is evident that the diagnosis is not difficult so long as one realizes that such a condition exists.

Several different forms of treatment have been used. They may be grouped in three divisions: puncture, incision and drainage, and excision.

In 1860, Rochard<sup>46</sup> found it necessary to incise and drain a hematocele sac of 2940 cc. after the injection of iodine had been unsuccessful in the treatment of the condition. In 1875, Steele<sup>10</sup> tapped and withdrew 900 cc. (30 ounces); he then allowed infection to occur, hoping to obliterate the cavity by this method, and the incisions finally healed. Trendelenburg<sup>11</sup> likewise used incision and drainage. Kocher employed puncture in 2 children and followed the procedure by the injection of tincture of iodine in 1; phlegmon of the scrotum developed in 1 of these cases. Witzel<sup>13</sup> used for drainage a groin incision rather than one over the scrotum. In 1896, Mikulicz performed a radical operation (excision) in the case reported by Vollbrecht.<sup>4</sup> Von Winiwarter,<sup>5</sup> in 1899, also found it necessary to excise a sac that had refilled following treatment by puncture. To ensure drainage, Bickle<sup>20</sup> stitched the edges of the sac to the skin edges. Excision has come to be the accepted procedure for permanent relief. Tapping is frequently followed by recurrence within a few months and, infrequently, by infection, which creates a surgical emergency. Incision is followed by a long period of drainage and is often complicated by infection.

Although the operative technic of excision can be very easy, certain writers have reported difficulties. Coleman<sup>28</sup> found it advisable to use a scrotal and an abdominal incision. Lasbrey<sup>22</sup> believed the sac to be retroperitoneal, and he used two incisions; there was some difficulty in removing the sac. Curtis,<sup>47</sup> who experienced difficulty with a laparotomy incision, was nevertheless able to complete the operation through a groin incision. In the commoner properitoneal type, a groin incision should allow for an easy extraperitoneal removal of both the abdominal and scrotal portions of the sac. In some, the atrophied testis has been removed. The defect in the abdominal wall following excision of the hydrocele mass should be repaired by the approximation of the conjoined tendon to the inguinal ligament. Most operators leave a small drain in the scrotal cavity. In addition, a tight compression bandage over the

lower abdomen and scrotum appears to be very advantageous in avoiding a large accumulation of serous fluid in the operative wound.

### CASE REPORT

L. R., a 25-year-old man, was admitted to the hospital because of a swollen scrotum. Swelling in the right scrotal region, which had first been noticed 8 years previously, had increased more rapidly during the preceding 2 years and had occasionally been painful. On admission there was some abdominal swelling, but this caused no inconvenience.

The patient's general health was good. There were no serious illnesses or operations and no history of injury.

On physical examination, a visible mass causing deformity of the abdominal wall was evident in the right lower quadrant (Figs. 6 and 7). This mass, which was

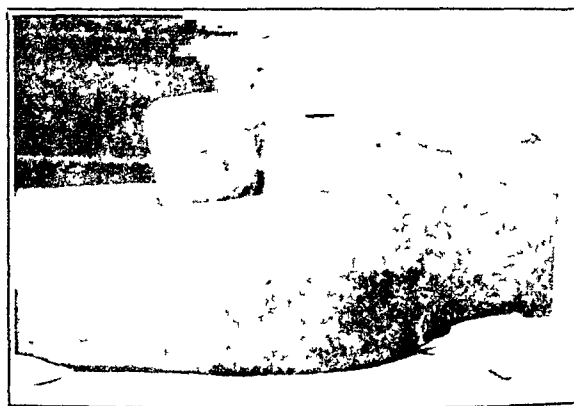


FIGURE 6 *Lateral View of a Patient with an Abdominoscrotal Hydrocele.*

smooth and firm, extended from above the level of the umbilicus to the scrotum, and from the region of the left rectus muscle well into the right flank. The abdominal mass seemed to be contiguous with a right scrotal swelling



FIGURE 7. *Semilateral View of a Patient with an Abdominoscrotal Hydrocele.*

which had the typical consistence of fluid. The scrotal mass was easily transilluminated. Palpation of the scrotal mass caused a fluid wave in the abdominal portion. The swelling was not tender. There was a definite impulse on coughing. A tentative diagnosis of abdominoscrotal hydrocele was made.

On February 12, 1941, under spinal anesthesia, an oblique incision was made over the right lower quadrant and upper part of the scrotum (Fig. 8). The upper part of the incision included the fibers of the external oblique

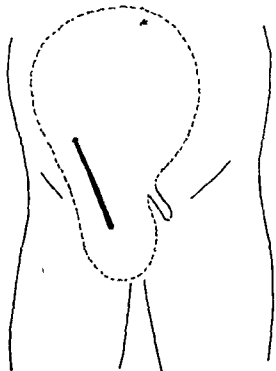


FIGURE 8. Diagram of the Abdominoscrotal Hydrocele and the Incision Used for Removal.

muscle and the conjoined tendons, and the lower part the usual layers of the scrotal wall. A good line of cleavage was found at the level of the enlarged cystic mass. The mass was easily enucleated by blunt and sharp dissection

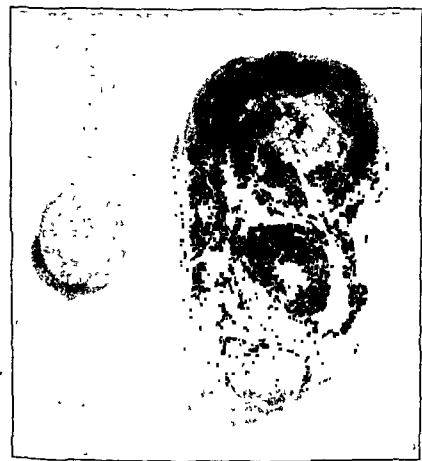


FIGURE 9. Photograph of the Excised Hydrocele Mass, Compared to a Large Lemon.

and was removed by being slid out through the incision, the scrotal part being first delivered. An atrophied spermatic cord was clamped and bisected. The operation was accomplished without opening of the sac or the peritoneal

cavity. The peritoneum was evident posterior to the hydrocele mass, but there was no evidence of any peritoneal reflection anterior to the mass. Fibers of the conjoined tendon and external oblique muscle were sutured to the inguinal ligament in an effort to support the lower abdominal wall. A small Penrose drain was left in the inguinal region, and one in the scrotal region. A firm

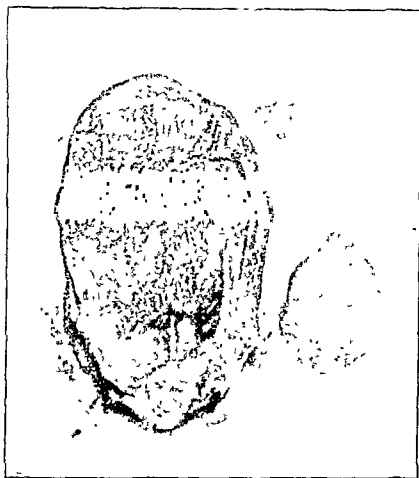


FIGURE 10. Hydrocele Sac Opened and Emptied, with a Small Testis at the Lower End.

compression bandage was applied to the lower abdominal and scrotal regions. Convalescence was uneventful.

The excised mass weighed 2600 gm. and contained 2000 cc. of olive colored fluid (Figs. 9 and 10).

#### SUMMARY

The literature on abdominoscrotal hydrocele is reviewed, and the condition is described. A report of a typical case, with a discussion of the operative technic employed, is presented.

29 Bay State Road

#### REFERENCES

- 1 Dupuytren, G. *Leçons orales de clinique chirurgicale*. Vol. 4. 765 pp. Paris: G. Ballière, 1834. P. 444.
- 2 Schmidt, J. Über Hydrocele bilocularis s. en bissac. *Centralbl. f. Chir.* 16:647, 1889.
- 3 Butz, R. Zur Casuistik d. hydrocele intraabdominalis bilocularis. *St. Petersburg, med. Wchnsch.* 4:440-442, 1887.
- 4 Vollbrecht, S. Über Hydrocele bilocularis intraabdominalis. *Arch. f. klin. Chir.* 52:223-250, 1896.
- 5 von Winwarter, F. Ein Fall von Hydrocele bilocularis. *Wien. klin. Wchnsch.* 12:1147-1149, 1899.
- 6 Fuchs, J. Zur Casuistik der Hydrocele bilocularis. *Wien. klin. Wchnsch.* 15:153, 1902.
- 7 Schütter, A. Über einen Fall von Hydrocele bilocularis intraabdominalis permagna. *München, med. Wchnsch.* 68:399-401, 1921.
- 8 Lister, J. On a remarkable case of hydrocele. *Edinburgh M. J.* 2:236-239, 1856.
- 9 Fano, M. Observation d'hydrocele de la tunique vaginale des deux côtés remontant jusque dans l'intérieur de la cavité abdominale, à travers le canal inguinal. *Bull. Soc. de Chir. de Paris* 4:294-302, 1853.
- 10 Steele, C. Enormous hydrocele situated in the abdomen, caused by undescended testis. *Lancet* 1:233, 1875.
- 11 Trendelenburg, F. Heilung der Hydrocele durch Schnitt und durch Drainage. *Berlin klin. Wchnsch.* 14:13-16, 1877.



12. Tillmanns, H. Ein Fall von intraabdominal Haematocoele. *Arch. f. klin. Chir.* 26:1009-1011, 1881.
13. Witzel, O. Beitrag zur Frage der Entstehung der Hydrocele bilocularis. *Centralbl. f. Chir.* 12:465-469, 1885.
14. Kocher, T. Hydrocele bilocularis abdominalis bei Kindern. *Centralbl. f. Chir.* 5:1-4, 1878.
15. Idem. Hydrocele (et Haematocoele) bilocularis intraabdominalis. In *Die Krankheiten der männlichen Geschlechtsorgane*. Lief. 50b of *Deutsche Chirurgie*. 640 pp. Stuttgart: Ferdinand Enke, 1887. P. 157.
16. Bazy, P. De l'hydrocèle vaginale à prolongement abdominal ou hydrocèle en bissac de Dupuytren. *Arch. gén. de méd.* 20:553 and 663, 1887.
17. Villeneuve, M. De l'hydrocèle en bissac. *Mercredi Méd.* 27:369-371, 1890.
18. Jacobson, W. H. A. *Diseases of the Male Organs of Generation*. 766 pp. Philadelphia: P. Blakiston's Son & Co., 1893.
19. Bickle, L. W. Abdominal or bilocular hydrocele. *Brit. M. J.* 2:13, 1919.
20. Idem. Double hydrocele in a youth. Operation for radical cure. *Australian M. Gaz.* 21:258, 1902.
21. Holmes, J. M. A case of properitoneal hydrocele. *Brit. J. Surg.* 20:346-348, 1932.
22. Lasbrey, F. O. A case of abdominal or bilocular hydrocele. *Brit. M. J.* 2:292, 1916.
23. Lewis, F. T., and Stöhr, P. *A Textbook of Histology Arranged upon an Histological Basis*. Second edition. 539 pp. Philadelphia: P. Blakiston's Son & Co., 1913.
24. Campbell, M. F. Hydrocele of the tunica vaginalis. *Surg., Gynec. & Obst.* 45:192-200, 1927.
25. Macewen, W. A contribution to the pathology of bilocular intrapelvic and scrotal hydroceles. *Practitioner* 57:123-135, 1896.
26. Tanzer, R. C. Abdominoscrotal hydrocele. *J. Urol.* 34:447-452, 1935.
27. Delbet, P. Des varietes de l'hydrocèle biloculaire. *Presse méd.* 4:421, 1896.
28. Coleman, R. B. Abdominal or bilocular hydrocele. *Brit. M. J.* 2:629, 1918.
29. Hubotter. Ein Fall von Hydrocele quadrilocularis intraabdominalis. *Berl. klin. Wchnschr.* 56:55, 1919.
30. Herbert, H. Hydrocele of the tunica vaginalis reaching within the abdomen. *Brit. M. J.* 1:844, 1893.
31. Lewtas, J. Properitoneal or abdominal hydrocele. *Lancet* 1:489, 1905.
32. Roller, C. S. Abdominoscrotal hydrocele. *J. A. M. A.* 103:671, 1934.
33. Richards, O. A case of double abdominal hydrocele. *Lancet* 2:533, 1908.
34. Parsons, H. H. Abdominoscrotal hydrocele hour-glass hydrocele. *Calif. formia & West. Med.* 42:266, 1935.
35. Lammert, J. Beitrag zur Kasuistik der bilokulären intraabdominellen Hydrocele. *Centralbl. f. Chir.* 16:646, 1889.
36. Cummins, A. G. Hydrocele en bissac. *J. Roy. Army M. Corps* 18:76, 1912.
37. Charters, A. D. Abdominal hydrocele with record of two cases. *Brit. M. J.* 1:470-472, 1935.
38. Firth, J. L. Bilocular intrapelvic and scrotal hydrocele. *Brit. M. J.* 2:1463, 1901.
39. Hermann, S. F. Abdominoscrotal hydrocele. *J. A. M. A.* 98:399, 1932.
40. Watson, F. S., and Cunningham, J. H., Jr. *Diseases and Surgery of the Genito Urinary System*. 2 vol. 1101 pp. Philadelphia: Lea & Febiger, 1908.
41. Sinford, H. L. Hydrocele, hematocele, spermatocele and varicocele. In Cabot, H. *Modern Urology*. Third edition. Vol. 1. 951 pp. Philadelphia: Lea & Febiger, 1936. Pp. 453-481.
42. Herman, L. *The Practice of Urology*. 923 pp. Philadelphia: W. B. Saunders Co., 1938.
43. Brandenburg, C. Cited by Schutter.<sup>7</sup>
44. Syme, J. Abdominal hydrocele. *Brit. M. J.* 2:139, 1861.
45. Wettergren, C. Hydrocele funiculi bilocularis extra et intraabdominalis. *Nord. med. Ark. (Kirurgi)* 3F:3 (No. 11):1-11, 1903.
46. Rochard, J. Note sur les hématoceles de la tunique vaginale qui remontent dans l'abdomen à travers le canal inguinal. *Union méd.* 7:359-363, 1860.
47. Curtis, C. S. Abdominoscrotal hydrocele. *J. A. M. A.* 99:467, 1932.

## THE USE OF DILANTIN SODIUM IN BRONCHIAL ASTHMA: A PRELIMINARY REPORT

MAURICE H. SHULMAN, M.D.\*

SALEM, MASSACHUSETTS

THE modern therapeutic armamentarium for the treatment of bronchial asthma is not satisfactory. Skin testing, with subsequent attempts to remove all suspected allergens, has not proved completely successful. The recent literature<sup>1-5</sup> has shown the importance of understanding the "asthmatic personality" and the role of psychogenic factors in bronchial asthma. The psychologic forces operating in this disease become more apparent when one is faced with the failures that occur under the present accepted medical regime. The search for a method of treatment that would exert its effect through nervous avenues and would be generally applicable led to the use of Dilantin Sodium in cases of bronchial asthma.

Sodium diphenyl-hydantoinate, commercially known as Dilantin Sodium, was described in 1937 and 1938 by Merritt and Putnam<sup>6,7</sup> as a new anti-convulsant. The same authors<sup>8</sup> later reported excellent results with this drug in the treatment of epilepsy. Dilantin Sodium has, up to the present time, been applied solely in the treatment of epilepsy. The literature reporting its successful use in this condition has grown voluminous. Merritt and Putnam<sup>9</sup> report that "in addition to a

relief or a great reduction in the frequency of the attacks, it was frequently noted by the parents of children that they were much better behaved, more amenable to discipline, and did better work in school." This improvement, they contend, must have been due in great part to the freedom from attacks, but they believe that the medication may also have produced other changes in the activity of the cerebral cortex. They continue with the statement that further study may conceivably lead to the use of Dilantin Sodium in conditions with similar cortical dysrhythmias other than those in the convulsive state.

After extensive use of Dilantin Sodium in epilepsy, Merritt and Putnam<sup>9</sup> discussed in detail the toxic effects, the great majority of which occur only when large doses are employed. The gastrointestinal symptoms of Dilantin Sodium intoxication were chiefly nausea and vomiting. Symptoms of toxic action of the drug on the central nervous system consisted of nervousness, tremor of the hands, drowsiness and headache, and ataxia. In 5 per cent of the patients, a toxic dermatitis varying from an erythema to a severe morbilliform rash appeared. Hypertrophy of the gums occurred, particularly in children and young adults. Those

\*Member of Pediatric Clinic, Outpatient Department, Salem Hospital; associate pediatrician, North Shore Babies' Hospital.

patients taking 0.3 gm ( $4\frac{1}{2}$  gr) or less daily showed few or no toxic symptoms.

As discussed above, it was decided to employ Dilantin Sodium for the treatment of bronchial asthma in a selected series of cases. Only patients with repeated, frequent, acute attacks of asthma and a constantly "wheezy" respiration were included in the series. Every attempt was made to choose intractable cases of asthma that had not responded favorably to routine and accepted treatment. No case of purely seasonal asthma was included.

The ages of selected patients varied from three to fourteen years. The group included 4 boys and 3 girls, all of the white race. The sex factor was entirely coincidental.

All the patients tested in this experimental series had been skin tested. They were all found to be sensitive to many different foods as well as to many other irritants. Moreover, at different periods, all had had attacks of asthma severe enough to require subcutaneous adrenalin. Routine treatment of bronchial asthma had, in all these cases, been followed for varying lengths of time, with indifferent results. Such treatment had been given in each case for at least a year and in some cases much longer.

Dilantin Sodium was administered to the patients described below for periods varying from five months to one year. The first step before treatment was begun was the complete elimination of all other medication. Since the entire literature on Dilantin Sodium deals exclusively with its use in epilepsy, it was necessary to develop an arbitrary system of dosage for the treatment of bronchial asthma. The problem of controlling the administration of the drug in this series was solved by dispensing a week's supply to each patient at his or her weekly visit. This resulted in complete co-operation from the patients, as well as effective control of the doses taken. Each patient was first given 0.03 gm ( $\frac{1}{2}$  gr) morning and night. Results were evaluated on the freedom from attacks and the absence of wheezing. If, after observation of one week under this dosage, symptoms still persisted, the patient was then given 0.03 gm ( $\frac{1}{2}$  gr) three times a day. Dosage was increased by 0.03 gm ( $\frac{1}{2}$  gr) daily at intervals of one week until the patient reported no attacks of asthma and no wheezing on moderate exertion. By this method of self titration, it was found that 0.1 to 0.2 gm ( $\frac{1}{2}$  to 3 gr) daily was sufficient to keep the patients symptom free.

Each patient was advised to take part in all activities. No attempt was made to keep the children from entering situations and places that had

previously precipitated attacks of bronchial asthma. In fact, as treatment with Dilantin Sodium progressed successfully, they were deliberately encouraged to enter such exciting and irritating environs as fairs, moving pictures, fairs, circuses, parties and active games. Unrestricted diets were prescribed. Living quarters were not changed and sleeping chambers were not specially prepared for the elimination of dust.

### CASE REPORTS

**CASE 1** E. K., a 5 year old girl, only child with no family history of allergy in infancy had severe eczema, which began to clear when she was about 2 years old. She was first seen at the age of 3 because of a persistent cough and wheeze following tonsillectomy. On examination a diagnosis of bronchial asthma was made. Subsequent attacks of asthma occurred at about weekly intervals. Routine skin testing showed positive reactions to many foods. No positive reactions were obtained when scratch tests were done with epidermids, grasses and weeds. The patient continued to have frequent attacks after the elimination of all known irritating factors; the medication consisted of ephedrine sulfate and allied drugs which gave partial relief. Over a period extending from April 1939, to July 1940, she had twenty four attacks of asthma severe enough to require injections of adrenalin in oil. All exciting play and activity had to be restricted because they apparently precipitated attacks. In July, 1940 the patient was first given Dilantin Sodium. After a few weeks of trial the dosage was established as 0.1 gm ( $\frac{1}{2}$  gr) morning and night. No severe asthmatic attacks have occurred since that time, and she leads an active, normal life. There has been occasional wheezing respiration, but this occurs so infrequently and is so mild that no other medication is required and her normal activities are not interrupted. There has been no change in her environment since she was first seen. She resides in the same house, and her sleeping quarters are the same. She observes no dietary restrictions. Her general physical condition is good, and her appetite unimpaired.

**CASE 2** P. M., a 14 year old girl, had a pronounced family history of asthma. Her father and her two brothers had bronchial asthma. The patient had eczema in infancy, which cleared. She was first seen in January, 1941, with an acute asthmatic attack. She had been having severe attacks about once each week for the previous 8 years. These attacks lasted 24 to 48 hours. For relief she had been taking ephedrine capsules as well as inhaling some powder that her father used. Incomplete skin testing showed a marked allergy to many foods and a strong reaction to ragweed and goldenrod. The patient appeared poorly nourished and was found to be 14 pounds under weight. She was listless and disinterested in all activities. Her schoolwork was poor. Dilantin Sodium—0.03 gm ( $\frac{1}{2}$  gr) morning and night—was ordered. With this dosage of the drug she had many mild attacks. The dosage was slowly increased to 0.1 gm ( $\frac{1}{2}$  gr) morning and night. The symptoms then disappeared. The patient had been able to take active part in winter sports and to skate, run and go out in cold and snowy weather—these activities had previously precipitated attacks. She has had several upper respiratory infections but no subsequent asthma or wheezing. Her schoolwork has improved, and her parents describe her general mental attitude as much brighter. There has been no restriction in diet.

and no change in environment. Her appetite is excellent, and she has gained 8 pounds in weight.

CASE 3. M. M., a 9-year-old boy, was seen because of frequent "colds and cough" for the previous 5 years. At the age of 6, he had a tonsillectomy, with no relief. For the past 2 years, he had had attacks of bronchial asthma at intervals of about 2 weeks. No family history of allergy could be obtained. When first seen in December, 1940, the patient was having a severe asthmatic attack and had difficulty in walking up a few steps. His chest was fixed, and his breathing noisy and labored. Complete skin testing revealed sensitivity to many foods, as well as to dust, chicken feathers and ragweed. He was given Dilantin Sodium in doses of 0.03 gm. ( $\frac{1}{2}$  gr.) morning and night. Wheezing continued until the dosage was increased to 0.03 gm. ( $\frac{1}{2}$  gr.) thrice a day. With this dosage, all symptoms disappeared until March, 1941, when the patient had a severe upper respiratory infection, with some wheezing. Prompt relief was obtained by increasing the dose of Dilantin Sodium to 0.06 gm. (1 gr.) morning and night. There have been no attacks and no wheezing since that time. His general physical condition has improved, and he has gained about 7 pounds. He is now able to take part in all active sports, and his family reports a marked lessening of irritability. His school grades and attendance record for this year are excellent as compared with those of the previous year. There has been no opportunity to observe the effect of Dilantin Sodium on his seasonal allergy.

CASE 4. G. A., a 10-year-old boy with no family history of allergy, had two attacks of lobar pneumonia in 1935, at 4 years of age. On recovery, he began to have attacks of bronchial asthma. He was first seen in 1937, when he was 6 years old, and was referred to a Boston hospital for treatment. Skin tests at that time revealed sensitivity to many foods, as well as to ragweed and grasses. Since then, the patient had received various kinds of treatment, including osteopathic manipulation. Attacks occurred at about weekly intervals, but the patient was never completely free of symptoms. Because of his constant asthma, his activities were so restricted that he was practically an invalid. In December, 1940, he was given 0.03 gm. ( $\frac{1}{2}$  gr.) Dilantin Sodium morning and night. It was necessary to increase the dosage rapidly to 0.1 gm. ( $\frac{1}{2}$  gr.) morning and night. Since the establishment of this dosage, the patient has had no attacks of bronchial asthma until the onset of his seasonal allergy. He has been able to take an active part in sports, and his schoolwork has shown marked improvement. He eats well and sleeps well. At present, he shows a gain of 8 pounds in weight. He is an entirely new personality, sparkling and lively. There has been no change in environment, and his diet is entirely unrestricted.

Since May, with the onset of this year's seasonal sensitivity to the grasses, he has had some wheezing and labored breathing, but no severe asthmatic attacks. Increasing the dose of Dilantin Sodium to 0.1 gm. ( $\frac{1}{2}$  gr.) thrice a day has had no appreciable effect. His present symptoms, however, are relatively mild and do not restrict his activities.

CASE 5. M. N., a six-year-old boy, had been seen at intervals since birth. Both his mother and father were allergic. From infancy, he had frequent attacks of spasmodic bronchitis, but otherwise his early history was essentially unremarkable. He had always been a high-strung, nervous boy—always a problem to control. He was pampered and markedly overprotected. In 1937, the patient had a severe case of pertussis. Convalescence was prolonged. Six

months after recovery, he developed pneumonia. Recovery was again prolonged and was immediately followed by attacks of severe bronchial asthma. These attacks occurred at about weekly intervals. The patient was seen by an allergist, and skin tests showed a mild sensitivity to some foods. No grasses or weeds gave positive results. Even with elimination diets and complicated attempts to avoid contact with suspected irritating allergens, combined with the administrations of ephedrine sulfate and other standard treatment, he had little if any relief. Any new or exciting situation seemed to precipitate an attack. He was much restricted in his play by the parents and was absent from school a great deal.

In March, 1941, treatment with Dilantin Sodium was begun, following a severe asthmatic attack. The boy was first given 0.03 gm. ( $\frac{1}{2}$  gr.) morning and night; this was found to be insufficient. In about 2 weeks, the dosage was increased to 0.03 gm. ( $\frac{1}{2}$  gr.) in the morning and 0.1 gm. ( $\frac{1}{2}$  gr.) at night. He began to take part in social and physical activities, and his attendance record at school was excellent. Three upper respiratory infections with hyperpyrexia occurred, but did not, in contradistinction to the past record, result in attacks of bronchial asthma.

At the end of 2 months of treatment, the patient developed what his mother called an asthmatic attack. During this attack, his breathing was labored and he wheezed, but no rales could be heard in the chest. All these symptoms were pronounced when the patient was being examined or discussed, but disappeared when his attention was occupied. He has had four or five such episodes since, none of which required special treatment. It was believed that these attacks were not true asthmatic attacks, but there is much evidence that they were used as a device to attract attention. Because of the parents' extreme anxiety about the boy, however, he was referred to an allergist and an otolaryngologist for further checkup.

CASE 6. P. B. F., a 4-year-old boy with a family history of allergy—his paternal uncles and his father had severe hay fever—had an obstinate infantile eczema. At about 3 years of age, he developed frequent attacks of bronchial asthma. Skin tests showed marked positive reactions to many foods, as well as to the grasses and weeds. Asthmatic attacks occurred throughout the entire year at about weekly intervals. A tonsillectomy was done in November, 1940. Convalescence was uneventful, and the patient had no asthmatic attacks until March, 1941. With the resumption of attacks of bronchial asthma at that time, Dilantin Sodium treatment was begun. The initial dose was 0.03 gm. ( $\frac{1}{2}$  gr.) morning and night. Some symptoms persisted until the patient was taking 0.1 gm. ( $\frac{1}{2}$  gr.) morning and night. At this dosage level, he was symptom free. Marked improvement was also noted in the residual eczema.

With the onset of his seasonal allergy,—caused by the grasses,—the patient's mother reported that he had moderate attacks of sneezing, morning and night. In an attempt to overcome these symptoms of vasomotor rhinitis, the dose of Dilantin Sodium was increased to 0.2 gm. (3 gr.) morning and night. This increase had little effect on the spasms of sneezing. One week after the patient began to take the 0.4 gm. (6 gr.) daily, he developed signs of central-nervous-system intoxication. He complained of dizziness, diplopia, nausea and vomiting, and a staggering gait was noticed. The drug was then discontinued for 5 days, during which he had several attacks of bronchial asthma. Dilantin Sodium was resumed in doses of 0.03 gm. ( $\frac{1}{2}$  gr.) morning and night. Complete

relief from asthmatic symptoms was not obtained until he was given 0.1 gm (1½ gr) morning and night. His spasms of sneezing persisted.

This child was always markedly overprotected and his activities greatly limited. His mother reported that he was always hyperactive, irritable and in some respects social. With the improvement in his asthmatic symptoms since taking Dilantin Sodium, he has been allowed more freedom of action and diet. At present he is much more pleasant and amenable.

**CASE 7.** D. R., a 3-year-old girl with no family history of allergy, had eczema which had persisted since early infancy. In November, 1940, this patient—an only child—was seen with an attack of bronchial asthma. Her mother denied any previous attacks. These attacks occurred at frequent intervals. Skin tests revealed sensitivity to many foods, but no reaction to the grasses and weeds. In January, 1941, the patient was started on 0.03 gm (½ gr) Dilantin Sodium morning and night. At weekly intervals the dose was increased to 0.1 gm (1½ gr) morning and night. At this level, the patient remained free of any asthmatic attacks for months. The eczema also improved markedly.

In May, the child's mother failed to return for her supply of Dilantin Sodium, and the patient remained without treatment for a week. At the end of that time, she was again seen with a moderately severe attack of bronchial asthma. Dilantin Sodium, 0.1 gm (1½ gr) morning and night was again given with complete cessation of symptoms. With this dosage, the patient has remained symptom free.

#### SUMMARY

Because of recent work on the psychogenic aspect of bronchial asthma and the concept of the so-called 'asthmatic personality,' a search was made for a drug that would have a psychosomatic effect on children with bronchial asthma. Recent work with Dilantin Sodium and its application in the treatment of epilepsy have amply proved this to be a powerful and efficient anticonvulsant. The infrequency of toxic effects, in addition to its reported effect of improvement in the epileptic personality, marked the drug as one worthy of trial in cases of bronchial asthma.

Seven cases of intractable, severe bronchial asthma were selected for treatment with Dilantin Sodium. These cases were skin tested and were found to be sensitive to many different allergens. The ages of the patients ranged from three to fourteen years. The sex factor was not controlled although in this series there were 4 boys and 3 girls. The patients received Dilantin Sodium for periods varying from five months to one year, although several were studied for a far greater length of time.

The dosage of Dilantin Sodium was determined for each patient by "self titration" methods. When adequate dosage was maintained, 6 patients remained consistently free from attacks of bronchial asthma. Two patients reported abortive at-

tacks, consisting of slight wheezing, which passed off rapidly. In only 1 case did toxic symptoms result from the ingestion of the drug. In this case, the toxic symptoms cleared rapidly on withdrawal of the drug, and the patient was able to resume treatment with a slightly smaller dose.

In 2 cases complicated by seasonal allergies, nasal and ocular symptoms of the allergy occurred and could not be controlled with Dilantin Sodium.

During the administration of the drug, there were no change in environment and no dietary restriction. During this period, some of the patients suffered acute upper respiratory infections, with no resulting bronchial asthma in sharp contrast with the previous history of these patients. To test the efficacy of Dilantin Sodium in controlling asthmatic attacks brought on by emotional upsets, many patients were encouraged to enter situations and environments that formerly precipitated attacks of bronchial asthma. With this drug as the sole medication, the patients were consistently free of attacks of bronchial asthma, and they were able to engage normally in athletic and social activities. In the 1 case in this series in which complete success was not obtained the lack of parental co-operation and understanding was an important factor.

Cases 2, 3 and 4 were marked by a distinct change in personality with lessening of irritability. The patients were reported to be much brighter mentally and much easier to live with. In Case 2 a distinct improvement in schoolwork was noted.

In 2 cases a stubborn eczema which had persisted since infancy cleared to a remarkable degree while the patients were taking Dilantin Sodium.

#### CONCLUSIONS

Dilantin Sodium gave marked relief in 6 of 7 cases of bronchial asthma.

The drug must be given continuously to prevent the attacks.

The modus operandi of this drug in cases of bronchial asthma cannot be determined from the results with this small group of patients.

Personality changes were observed in these patients.

Concomitant eczema improved with the administration of Dilantin Sodium in 2 cases.

A new field of investigation which requires much more clinical and laboratory work with Dilantin Sodium in bronchial asthma is open.

40 Washington Square

#### REFERENCES

1. Raper, C. H., Harless, D. H., and Duguid, K. A. Psychologic approach to the problem of asthma and the asthma-eczema prurigo syndrome. *Cuy & Hosp. Rep.* 55: 749-758, 1935.
2. S. R. S. F. D. The psychogenic factor in asthma. *Cuy & Hosp. R. P.* 55: 1019-1015, 1935.

3. Rogerson, C. H. The psychological factors in asthma-prurigo. *Quart. J. Med.* 6:367-394, 1937.
4. McDermott, N. T., and Cobb, S. A psychiatric survey of fifty cases of bronchial asthma. *Psychosom. Med.* 1:203-244, 1939.
5. Hall, M. B. Asthma in childhood: a discussion of the psychological aspect. *Brit. M. J.* 2:110-113, 1940.
6. Putnam, T. J., and Merritt, H. H. Experimental determination of the anticonvulsant properties of some phenyl derivatives. *Science* 85:525, 1937.

7. Merritt, H. H., and Putnam, T. J. A new series of anticonvulsant drugs tested by experiments on animals. *Arch. Neurol. & Psychiat.* 39:1003-1015, 1938.
8. *Idem.* Sodium diphenyl hydantoinate in the treatment of convulsive disorders. *J. A. M. A.* 111:1068-1073, 1938.
9. *Idem.* Sodium diphenyl hydantoinate in treatment of convulsive seizures: toxic symptoms and their prevention. *Arch. Neurol. & Psychiat.* 42:1053-1058, 1939.

## CLINICAL NOTE

### THE ASSOCIATION OF PRIMARY NEOPLASM OF THE LIVER WITH HEMOCHROMATOSIS\*

REPORT OF A CASE

ERNEST W. SAWARD, M.D.†

BOSTON

IT IS widely recognized that the severer grades of diffuse hepatic cirrhosis are frequently complicated by a primary hepatic neoplasm. Counselor and McIndoe<sup>1</sup> reported 5 such cases in 127 cases of portal cirrhosis, an incidence of 3.9 per cent. Stewart<sup>2</sup> collected 9 cases in 120 cases of well-marked cirrhosis, an incidence of 7.3 per cent. The first authors even suggest that primary carcinoma of the liver develops in 3 to 4 per cent of patients with cirrhosis.

This type of neoplasm also occurs in association with another type of cirrhosis, namely hemochromatosis. In this disease, the fibrosis is believed to result from the reaction to a diffuse deposit of hemosiderin throughout the liver and other organs. Sheldon,<sup>3</sup> in his excellent monograph on hemochromatosis, published in 1935, collected from the literature 345 cases in which 20 patients had primary cancer of the liver, an incidence of 5.8 per cent. This is in agreement with the figures for cirrhosis in general.

The following case of hemochromatosis is reported as an example of this interesting association with hepatoma.

#### CASE REPORT

G. M. (P. B. B. H. Medical 59247), a 62-year-old married man, entered the medical service of the hospital on March 16, 1941, with the complaint of weakness. For several years, he had noticed gradually increasing pigmentation of his skin, without other symptoms. Three months before entry, he noticed a rather sudden onset of weakness, anorexia, polydipsia and polyuria, and was found to have glycosuria by his local physician. He was regulated satisfactorily by dietary management with 22 units of protamine insulin and 30 units of regular insulin every morning. Two weeks prior to entry, the patient noticed marked

weakness in his left arm and leg and soon became unable to raise his left hand.

The family history was noncontributory. He had enjoyed excellent health until his present illness. He did not use alcohol, and he had not been exposed to any occupational hazard.

Examination showed a well-developed, moderately obese and chronically ill elderly man. The skin was generally pigmented brown, most markedly on the forearms and



FIGURE 1. Photograph of a Section of the Liver, Showing Fibrosis and the Deposition of Hemosiderin.

abdomen. There was slight pigmentation of the oral mucous membranes and at the angles of the lips. Body and axillary hair was scant, and the pubic hair was of the female configuration. The blood pressure was 96/50; 6 weeks previously, it had been 140/70. The heart was not enlarged, the rate and rhythm were normal, the sounds were distant, and no murmurs were heard. The lungs were clear. The liver edge was felt 4 cm. below the right costal margin and was smooth and firm. There was no free fluid in the abdomen. The cranial nerves were intact, but there was marked weakness of the left arm and leg. Sensation was unimpaired. The tendon reflexes were slightly diminished on the left side. There was no Babinski sign on either side.

The blood Hinton reaction was negative. Examination of the blood showed a red-cell count of 4,590,000 with a hemoglobin of 100 per cent (Sahli), and a white-cell count of 10,000. Urine analysis showed a +++ test for sugar, but no acetone. Blood chemical findings were a nonprotein nitrogen of 27 mg., a sugar of 218 mg., a cholesterol of 170 mg. and a serum protein of 7.5 gm. per 100 cc., with an albumin of 3.7 gm. and a globulin of 3.8 gm. per 100 cc. The carbon dioxide combining power was 20 milliequiv. per liter, the sodium 127 milliequiv. per liter, the icteric index 17, and the sedimentation rate 5 mm. per hour. A bromsulphalein liver-function test showed 90 per cent retention in 30 minutes. The vital

\*From the Medical Clinic, Peter Bent Brigham Hospital.

†Formerly, assistant resident physician, Peter Bent Brigham Hospital.

capacity was 1700 cc. The basal metabolic rate was -2 per cent. An electrocardiogram showed low voltage, premature auricular beats and a very small R wave in Lead 4F.

The clinical course was afebrile except on one occasion, when there was a rise in temperature to 101°F. Because of the symptoms of weakness and nausea and the findings

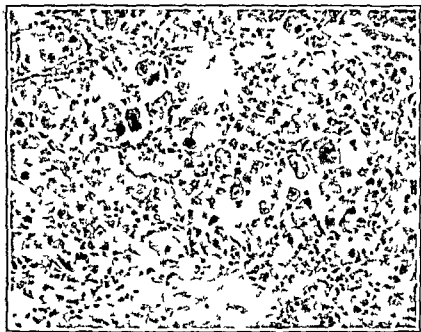


FIGURE 2 Photograph of a Section of the Hepatoma

of low blood pressure, pigmentation of the oral mucous membranes and low blood sodium, the possibility of a concurrent adrenal insufficiency was considered. Accord-

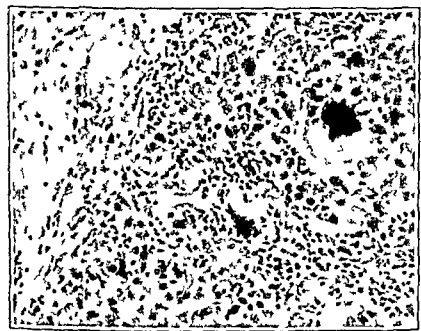


FIGURE 3 Photograph of a Section of a Metastasis in the Adrenal Gland

ingly sodium chloride was added to the diet, and 70 mg per day of desoxycorticosterone acetate was administered intramuscularly. The patient became weaker, and neither the blood pressure nor the blood sodium rose. Despite 50 units of regular insulin daily, the blood sugar rose to 450 mg per 100 cc. Cheyne-Stokes respirations became apparent, and the venous pressure increased to the equivalent of 240 mm of water. The patient was rapidly digitalized. On the 6th hospital day, acute pulmonary edema developed, and the patient expired while a phlebectomy was being attempted.

**Autopsy.** The principal findings at autopsy consisted in hemochromatosis, with marked atrophy and fibrosis of the pancreas, cirrhosis of the liver and malignant hepa-

toma (Fig 1). The last had metastasized to the lymph nodes at the hepatic hilus and to the right cerebral hemisphere (Fig 2). No lung metastases were seen. Pigment deposits consisting predominantly of hemosiderin and to a lesser extent of hemofuscin were present in all organs. They were most abundant in the pancreas, liver and lymph nodes. The heart and particularly the parathyroid, thyroid and pituitary glands, epididymis and choroid plexus represented other sites of marked pigmentation. The adrenal glands displayed a fair degree of pigmentation (Fig 3) but were not otherwise histologically unusual. The heart weighed 380 gm, the liver 2560 gm, and the pancreas 160 gm. The tumor in the liver measured 4 by 5 by 7 cm, and the metastatic nodule in the brain was 11 cm in diameter (Fig 4).

Inasmuch as the presence of the hepatoma was unsuspected clinically in this case, the discovery that the cerebral metastases accounted for the hemiplegic symptoms was doubly surprising. Involvement of the brain by metastasis from a liver-



FIGURE 4 Photograph of a Section of a Metastasis in the Brain

cell carcinoma is unusual. Of 33 cases of hepatoma with ordinary cirrhosis and 17 with hemochromatosis reported by Stewart,<sup>2</sup> none had secondary involvement of the brain by the tumor.

Adrenal insufficiency was suggested clinically by asthenia, nausea, low blood pressure, low blood sodium and pigmentation of the oral mucous membranes, in addition to the pigmentation of the skin. Lack of response to salt and desoxycorticosterone therapy, however, as well as the only slightly altered histologic appearance of the adrenal glands at autopsy, made this uncertain. The role of other endocrine gland changes in the production of symptoms in this disease has led to speculation. Butt and Wilder<sup>4</sup> suggest that impotence and atrophy of the hair and skin may be due to a deposition of hemosiderin in the anterior lobe of the hypophysis. To explain the pigmenta-

tion of the oral mucous membranes, these authors suggest a deposit of melanin secondary to the involvement of the adrenal gland by hemosiderin. These hormonal interrelations are of interest but are difficult to analyze.

### SUMMARY

A case of hemochromatosis is reported in which a primary hepatoma with metastasis to the brain occurred. The relation of hepatoma to hemochromatosis is discussed. Some of the clinical features

of this case could be attributed to adrenal insufficiency.

I am indebted to Dr. Orville T. Bailey for the photographs used in this report.

### REFERENCES

1. Counseller, V. S., and McIndoe, A. H. Primary carcinoma of the liver. *Arch. Int. Med.* 37:363-387, 1926.
2. Stewart, M. J. Precancerous lesions of the alimentary tract. *Lancet* 2:565-572, 1931.
3. Sheldon, J. H. *Haemochromatosis*. 382 pp. New York and London: Oxford University Press, 1935.
4. Butt, H. R., and Wilder, R. M. Hemochromatosis: report of thirty cases in which the diagnosis was made during life. *Arch. Path.* 26:262-273, 1938.

## MEDICAL PROGRESS

### TOXIC REACTIONS FOLLOWING SULFONAMIDE TREATMENT\*

CHESTER S. KEEFER, M.D.†

BOSTON

THAT toxic reactions follow the use of the various sulfonamides is well known. That they vary in their frequency and severity, as well as in their clinical features, is also well recognized. The purpose of this report is to summarize the various toxic reactions as they are observed in patients following sulfonamide treatment, and to discuss their significance.

For purposes of discussion, the toxic reactions can be divided into several groups in accordance with the system involved and the time of their occurrence (Fig. 1). Toxic reactions referable to the gastrointestinal tract, the hematopoietic and the renal systems are the most important and frequent. The time of their occurrence may be divided into the prompt, the accelerated and the delayed reactions. Although there is very little information available concerning the precise mechanism of the production of side effects, it seems clear that some of the reactions are due to the direct toxic effect of the drugs on tissues, whereas others are due to hypersensitive reactions that are similar in many respects to drug hypersensitivity in general.

### SKIN REACTIONS

Among the common untoward reactions to the sulfonamides are various skin eruptions. They are

characterized by their pleomorphism, and are frequently accompanied by other signs of drug intoxication or hypersensitivity. They vary in frequency with different drugs (Table 1), and they are often widespread in distribution. The lesions cannot be inhibited by the administration of para-aminobenzoic acid. There is nothing distinctive about the eruptions, since they may be erythematous, morbilliform, urticarial or purpuric, and in some cases a generalized exfoliative dermatitis, with massive edema, appears. Lesions resembling erythema nodosum are most frequently seen following sulfathiazole therapy. One of the curious features of some of the cases of dermatitis, especially those following sulfanilamide, is the fact that the eruption develops after exposure to sunlight or, at least, is made worse following such exposure.

The skin eruptions occur at one of three periods following the administration of the drugs. The usual time is between seven and nine days after the drug is started, although the lesions may appear as early as the fourth day or as late as the fourteenth day (delayed reaction). They may occur, however, as a prompt or accelerated reaction within twenty-four hours after the drug has been started, or as late as two to six weeks. When the skin eruptions are prompt or accelerated, they almost invariably occur in persons who have previously received the same or a closely related drug. For example, the usual story is that they received the same or a different sulfonamide at some time in the past, and that a reaction consequently followed within seven to fourteen days. This delayed reaction, which was self-limited in duration, disappeared following withdrawal of the drug. Then,

Reprints of articles in this series are not available for distribution, but the articles will be published in book form. The current volume is *Medical Progress: Annual, 1940* (Springfield, Illinois: Charles C Thomas Company, 1941. \$4.00).

\*From the Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine.

†Director, Evans Memorial, and physician-in-chief, Massachusetts Memorial Hospitals; Wade Professor of Medicine, Boston University School of Medicine.

after an interval varying from a few days to months or even several years, the same drug or a different one is given, with a prompt reaction. The prompt reactions may occur after single small

who have previously had the drug without any noticeable reactions. Patients who have acquired sensitivity to sulfapyridine may react in a similar manner to sulfamethylthiazole or sulfapyridine

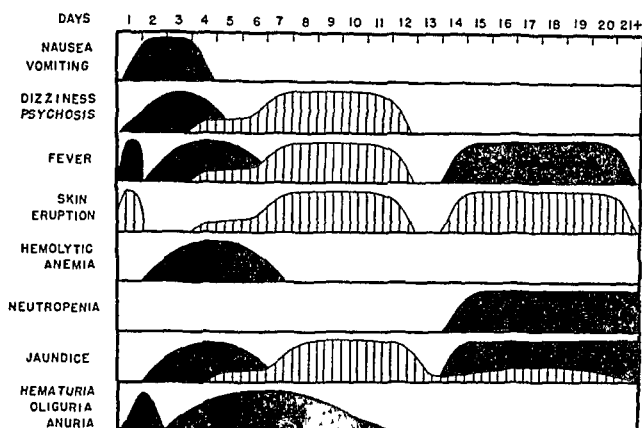


FIGURE 1. Chart Showing the Time of Appearance of the Various Toxic Manifestations of the Sulfonamides.

The vertically hatched areas represent skin eruptions; they are superimposed on the lines indicating other toxic manifestations to demonstrate the possible co-existence of complications.

doses, and they may be more extensive and serious than the previous reactions, since they are sometimes associated with exfoliative dermatitis or

but not to sulfanilamide, and patients who are sensitive to the esters of para-aminobenzoic acid (procaine hydrochloride) may be sensitive to sul-

TABLE 1. Frequency of Toxic Reactions Following Various Sulfonamides.

TOXIC REACTION	SULFANILAMIDE	SULFAPYRIDINE	SULFATHIAZOLE	SULFAGUANIDINE	SULFADIAZINE
Nausea or vomiting, or both	10-20%	40-55%	23-40%	2-5%	5-9%
Mental disturbances including toxic psychoses	0.5-1%	0.3-5%	0-2%	0	0
Skin eruption	2-5%	4-5%	8-10%	Occasional	2-3%
Fever	10%	2-5%	5-6%	Occasional	1%
Anemia	1-2%	2-3%	Very rare	Not reported	Not reported
Leukopenia	0.1%	0.1-0.5%	Rare	Not reported	2%
Hematuria	0	2-3%	2-3%	Not reported	0.5-1%
Oliguria	0	0.1-0.5%	0.5-1%	Not reported	0.5-1%
Anuria, with nitrogen retention	0	Not reported	0.5-1%	Not reported	0.5-1%
Jaundice	Rare	Not reported	Rare	Not reported	Not reported
Hepatitis	Rare	Not reported	Rare	Not reported	Not reported
Purpura hemorrhagica	Rare	Rare	Not reported	Not reported	Not reported
Gastrointestinal bleeding	Occasional	Occasional	Not reported	Not reported	Not reported
Stomatitis	Rare	Rare	Not reported	Not reported	Not reported

the signs of toxic hepatitis. Although these prompt or accelerated reactions occur oftenest in patients who have had reactions following the first experience with the drug, they may appear in those

fanilamide (para-aminobenzoic sulfonamide). It is plain, then, that the hypersensitivity to the drug may be specific, and that the reactions may follow the exhibition of a closely related drug. This



suggests that there is a common substance in the various drugs to which some patients become sensitive.

In most cases, the prompt hypersensitive skin eruptions are accompanied by fever, and in some, they may be associated with such features as toxic hepatitis.

Delayed skin eruptions, which were first described by Hageman and Blake, occur commonly between the seventh and the ninth day after the drug is started, and fever is associated with the eruption in about half the cases. The fever may subside within two to seven days after the drug is withdrawn, but the skin eruptions may persist for several weeks or even longer. Other associated features are generalized edema, enlargement of the lymph nodes, leukocytosis (often reaching a count of 70,000 or 80,000), transient jaundice without anemia, and eosinophilia (20 to 55 per cent). The delayed skin eruptions may also be a feature in the patients with neutropenia or in the cases of jaundice occurring as late as the sixth week after the drug has been discontinued.

#### FEVER

Febrile reactions following the sulfonamides may be prompt, accelerated or delayed. They may occur alone, with a skin eruption, or with other manifestations of drug intoxication or hypersensitivity. They may be superimposed on the fever of infection, or they may appear after the fever of infection has disappeared. In a few cases, they occur several days after the drug has been discontinued. These episodes are usually self-limited and last from two to nine days, the usual duration being two to four days. They occur with varying frequency following the different sulfonamides and are commonest after sulfathiazole and least common following sulfadiazine (Table 1).

Patients who develop febrile reactions within the first twenty-four hours have almost invariably received the drug previously, with or without signs of intoxication. When the fever develops or is increased within two to six days following its exhibition, there is generally an associated hemolytic anemia.

Prompt febrile reactions following a single dose of the sulfonamides may be an isolated feature, or they may be followed or accompanied by a skin eruption, toxic hepatitis, leukopenia or hemolytic jaundice.

The onset of the fever may be very abrupt and accompanied by a chill and a skin eruption. Such reactions usually follow the repeated use of the same or a related drug, although a patient may be

sensitive to one and not to another. Dowling has reported that a patient who reacted to a second dose of sulfadiazine failed to react to sulfathiazole, sulfapyridine or sulfanilamide. Davidson and Bullowa reported a case in which fever and a skin eruption followed the use of sulfapyridine or sulfamethylthiazole in a patient with acquired sensitivity to sulfapyridine; the same patient, however, failed to react to sulfanilamide.

#### RENAL COMPLICATIONS

Three renal complications may follow the use of the sulfonamides: hematuria, renal colic, and oliguria or anuria. They have been described following sulfapyridine, sulfathiazole and sulfadiazine, but not after sulfanilamide (Table 1). To understand these phenomena, one must be familiar with the facts concerning the excretion of the free and combined or acetylated sulfonamides by the kidney. It is now firmly established that, once the various sulfonamides are absorbed from the gastrointestinal tract, a part of the drug remains free and the remainder is changed by the process of acetylation to the combined form, and both fractions are excreted almost quantitatively by the kidney. The acetylated drugs are more insoluble than the nonacetylated, so that when the urine is concentrated by reabsorption of water by the kidney tubules the precipitation of the acetylated compounds is likelier to occur than that of the free compounds. The crystals may form in the tubules or the pelvis of the kidney, or they may precipitate out in the ureters or the bladder; in either event, they cause obstruction to the free flow of urine, and oliguria or anuria may follow. This may be preceded by attacks of renal colic or hematuria, or both. The hematuria is not always associated with renal colic, and may occur without any of the signs of obstruction. In these cases, it is difficult to escape the conclusion that there has been actual irritation of the glomeruli. When there is oliguria or anuria, the nonprotein nitrogen of the blood increases, and signs of renal insufficiency and even uremia may follow. It is rare indeed for any patient who has shown symptoms and signs of renal insufficiency during sulfonamide therapy to continue to show them following the discontinuation of treatment, unless the kidneys have been insufficient prior to the drug treatment. In other words, if permanent renal damage ever occurs from sulfonamide treatment, it must be exceedingly rare.

From what has been said, it is apparent that the concentration of the urine, the duration of treatment and the functional capacity of the kidney prior to administration of the drug are all impor-

tant considerations in the renal complications of sulfonamide therapy.

Hematuria, which is the commonest manifestation of renal irritation, may occur as an isolated feature or in association with renal colic. It is more frequently seen after sulfapyridine than after sulfathiazole or sulfadiazine, probably owing to the variation in the amount of drug acetylated before it is excreted by the kidney. Hematuria may occur as early as the first day of treatment in patients receiving intravenous therapy, but, as a rule, it is seen on the second and third days, or later. In several reported cases, renal colic and hematuria appeared several days after the drug had been discontinued, probably because the fluid excretion was decreased before all the drug had been eliminated from the body. Generally speaking, hematuria disappears following discontinuation of the drug and the forcing of fluids to 2500 cc daily.

When the fluid intake is inadequate because of vomiting, stupor or the intoxication accompanying the infection, or when renal insufficiency precedes the use of the drugs, oliguria and even anuria may occur. When the sodium salts are given intravenously, hematuria and oliguria may be seen within twenty-four to forty-eight hours. In most cases, however, oliguria is first noticeable after the drug has been given for several days. It is for this reason that the fluid intake and urinary output should be watched carefully so long as the drug is being given. Nitrogen retention accompanies the oliguria, and in many cases, the symptoms and signs of uremia develop. If any of these signs appear, the drug should be discontinued at once, the fluid intake increased to at least 3000 cc a day, and cystoscopy carried out to ascertain whether there is an obstruction of the ureters. Aside from agranulocytosis, the renal complications are the most serious and require prompt action if they occur during the course of the treatment.

#### JAUNDICE

Following the use of the sulfonamides, particularly sulfanilamide, jaundice is occasionally encountered, owing to the development of a hemolytic anemia or a toxic hepatitis. Associated with the jaundice, there may be an exfoliative dermatitis, other skin eruptions or neutropenia. The time of the appearance of the jaundice is significant. It may be accelerated or delayed. During the first week of treatment, icterus usually signifies a hemolytic anemia.

When delayed, the jaundice may appear between the eighth and the fourteenth day, or even later. It is accompanied in most cases by exfoliative

dermatitis—occasionally, by neutropenia. One case has been reported by Garvin in which jaundice and exfoliative dermatitis were observed six weeks after the drug had been discontinued.

In the cases associated with the signs of hemolytic anemia, the jaundice is due to increased blood destruction as well as to toxic hepatitis, since bilirubin appears in the urine and the bromsulfalein test usually shows retention of dye. Watson and Spink have demonstrated impaired liver function following the administration of sulfanilamide.

When jaundice without anemia occurs within a few days after the drug is started, this usually means that the patient has been sensitized to the drug by a previous experience with it. As a rule, there was some sign of intoxication during the first course of treatment, but the signs of intoxication may have been absent. It is well to remember, as previously mentioned, that sensitization may occur without causing symptoms or signs at the time, the only evidence of sensitization appearing after the second exhibition of the drug at a later date. Cases have been observed in which jaundice followed a small amount of the drug, and was preceded by a chill, high fever and a skin eruption. Patients who have previously shown signs of hypersensitivity should never be given the drug a second time.

Enlargement of the liver and spleen and, in occasional cases, ascites accompany the jaundice. In most of the reported cases of toxic hepatitis, the prognosis is favorable, although it is poor when exfoliative dermatitis or neutropenia is also present.

#### ANEMIA

Anemia following the sulfonamides is of two types: acute hemolytic and slowly progressive. It is most frequent after sulfanilamide, but it may occur after any of the drugs (Table I). Harvey and Janeway were the first to report acute hemolytic anemia following sulfanilamide, and since then it has been observed with varying frequency in different clinics. Wood states that 24 per cent of adults and 8.3 per cent of children developed acute hemolytic anemia following sulfanilamide. This is the highest recorded incidence of this complication, but it serves to stress its importance.

Briefly, the course of the acute hemolytic anemia is as follows. Within one to seven days after sulfanilamide is started, the patient begins to complain of nausea and dizziness. There is commonly an exacerbation or an onset of fever. Within a short time, the patient becomes pale and sometimes icteric because of the rapid destruction of blood. The blood shows an anemia, with leuko-

cytosis; there are urobilinogenuria, bilirubinemia and, in some cases, hemoglobinemia and hemoglobinuria. Following the discontinuance of the drug, the forcing of fluids, and blood transfusions, recovery occurs in most cases, although the anemia may persist for as long as two to four weeks.

The leukocytosis may be very high with a leukemoid reaction; that is, the white-cell count may be well above 100,000, and nucleated red blood cells and myelocytes may be present in increased numbers.

From the studies of Watson and Spink, as well as those of Ham and of Antopol, Goldman and Sampson, it is now evident that profound changes occur in the hemoglobin metabolism and in the red blood cells of patients receiving sulfanilamide. Evidence of increased blood destruction and changes in the fragility to varying concentrations of salt solutions has been obtained, and suggests that sulfanilamide in some mysterious way makes the red blood cells vulnerable to rapid destruction. At the same time, it has a profound effect in the bone marrow, causing the changes that are responsible for the hyperleukocytosis with leukemoid reaction.

Of great significance is the observation that a recurrence of the anemia may follow the second course of the drug.

The second type of anemia, namely, the slowly progressive form, is exceedingly common in patients who receive large amounts of the sulfonamides for two weeks or longer. This type is difficult to interpret, since the infections that are being treated are often contributory. There seems to be no doubt that the anemia in many of these cases is due to the sulfonamides, since it occurs in patients with infections, such as gonococcal arthritis, that in themselves do not produce anemia. Some of these patients show splenomegaly. In any case, therefore, it is well to remember that a slowly progressive anemia is common following sulfonamide treatment, and that adequate means should be taken to recognize and treat it.

#### NEUTROPENIA AND AGRANULOCYTOSIS

A decrease in the total leukocyte count below 5000, with or without a corresponding decrease in the granulocytic cells, is not too uncommon following sulfonamide treatment. It is most frequently observed following sulfanilamide, and less often following sulfapyridine and sulfathiazole (Table 1). Although leukopenia is not infrequent after sulfadiazine, agranulocytosis must be rare, since, so far as I can determine, it has not been reported.

When agranulocytosis appears, it is a most serious complication: about 70 per cent of patients die. The usual time of its occurrence is between the fourteenth and the twenty-first day after the drug has been started, and it is most frequent in patients who have received a large amount of the drug continuously for that length of time. Occasionally, agranulocytosis is observed as early as the sixth or as late as the thirty-fifth day. In a few cases, it appears within a few days to two weeks after the drug has been discontinued. Once leukopenia occurs and the patient recovers, neutropenia and fever frequently develop following the second attempt to resume treatment. This was a feature of the case described by Jones and Miller.

The onset of agranulocytosis is usually accompanied by fever, sore throat, ulcerative stomatitis and pharyngitis, and a skin eruption. In a few patients, jaundice develops. Other signs of drug intoxication often precede the onset of agranulocytosis, such as skin eruptions, fever, anemia, jaundice and leukopenia. When these features appear, treatment should immediately cease.

The course of agranulocytosis is usually rapidly fatal in at least 70 per cent of all cases, and death occurs between four and six days following the onset of symptoms. The treatment consists in stopping the drug, the use of Pentnucleotide and blood transfusions, and the local treatment of the throat infection. This subject has been adequately reviewed in a recent progress report by Jackson.

#### MISCELLANEOUS AND INFREQUENT SIGNS OF INTOXICATION

##### *Ocular Lesions*

The following affections of the eyes have been observed: conjunctivitis and scleritis, acute myopia, optic neuritis and yellow vision. Conjunctivitis and scleritis are encountered following sulfathiazole. Acute myopia has followed sulfapyridine, with edema of the lens. Temporary optic neuritis has been described after sulfanilamide, and yellow vision was complained of by one of Dowling's patients following sulfadiazine. All these disturbances are temporary and subside when the drug is withdrawn.

##### *Symptoms Referable to the Central Nervous System*

*Psychoses.* Irritability, drowsiness and stupor, with mental depression, disorientation as to time and place, and hallucinations, are not infrequently encountered during treatment with the sulfonamides, and disappear rapidly once the drug is discontinued. The relative effect of the infection itself

and of the drug in causing the mental symptoms is sometimes difficult to assess, since many patients with pneumonia or other febrile illnesses ordinarily develop delirium or other signs of mental disturbance during their infections. There is no doubt, however, that the sulfonamides contribute to the production of temporary mental disturbances in some cases, since their withdrawal is followed by the disappearance of these symptoms.

**Polyneuritis.** A rare complication of sulfonamide treatment is polyneuritis, especially after sulfanilamide or sulfathiazole. In most of the reported cases, the drug was given in large amounts over a period of several weeks. The prognosis is usually good, although at least several months may be required for the patient to recover.

**Thrombopenic Purpura Hemorrhagica**

This is a rare complication of sulfanilamide or sulfapyridine intoxication, and one that should call for immediate discontinuation of the drug. On the whole, the prognosis is good following withdrawal of the drug.

78 East Concord Street

**BIBLIOGRAPHY**

**SKIN REACTIONS AND FEVER**

Davidson A and Bullows J G M Acquired hypersensitivity to sulfapyridine and sulfamethylthiazole *New Eng J Med* 223 811 813 1940  
Finney J A <sup>1</sup> <sup>2</sup> <sup>3</sup> <sup>4</sup> <sup>5</sup> <sup>6</sup> <sup>7</sup> <sup>8</sup> <sup>9</sup> <sup>10</sup> <sup>11</sup> <sup>12</sup> <sup>13</sup> <sup>14</sup> <sup>15</sup> <sup>16</sup> <sup>17</sup> <sup>18</sup> <sup>19</sup> <sup>20</sup> <sup>21</sup> <sup>22</sup> <sup>23</sup> <sup>24</sup> <sup>25</sup> <sup>26</sup> <sup>27</sup> <sup>28</sup> <sup>29</sup> <sup>30</sup> <sup>31</sup> <sup>32</sup> <sup>33</sup> <sup>34</sup> <sup>35</sup> <sup>36</sup> <sup>37</sup> <sup>38</sup> <sup>39</sup> <sup>40</sup> <sup>41</sup> <sup>42</sup> <sup>43</sup> <sup>44</sup> <sup>45</sup> <sup>46</sup> <sup>47</sup> <sup>48</sup> <sup>49</sup> <sup>50</sup> <sup>51</sup> <sup>52</sup> <sup>53</sup> <sup>54</sup> <sup>55</sup> <sup>56</sup> <sup>57</sup> <sup>58</sup> <sup>59</sup> <sup>60</sup> <sup>61</sup> <sup>62</sup> <sup>63</sup> <sup>64</sup> <sup>65</sup> <sup>66</sup> <sup>67</sup> <sup>68</sup> <sup>69</sup> <sup>70</sup> <sup>71</sup> <sup>72</sup> <sup>73</sup> <sup>74</sup> <sup>75</sup> <sup>76</sup> <sup>77</sup> <sup>78</sup> <sup>79</sup> <sup>80</sup> <sup>81</sup> <sup>82</sup> <sup>83</sup> <sup>84</sup> <sup>85</sup> <sup>86</sup> <sup>87</sup> <sup>88</sup> <sup>89</sup> <sup>90</sup> <sup>91</sup> <sup>92</sup> <sup>93</sup> <sup>94</sup> <sup>95</sup> <sup>96</sup> <sup>97</sup> <sup>98</sup> <sup>99</sup> <sup>100</sup> <sup>101</sup> <sup>102</sup> <sup>103</sup> <sup>104</sup> <sup>105</sup> <sup>106</sup> <sup>107</sup> <sup>108</sup> <sup>109</sup> <sup>110</sup> <sup>111</sup> <sup>112</sup> <sup>113</sup> <sup>114</sup> <sup>115</sup> <sup>116</sup> <sup>117</sup> <sup>118</sup> <sup>119</sup> <sup>120</sup> <sup>121</sup> <sup>122</sup> <sup>123</sup> <sup>124</sup> <sup>125</sup> <sup>126</sup> <sup>127</sup> <sup>128</sup> <sup>129</sup> <sup>130</sup> <sup>131</sup> <sup>132</sup> <sup>133</sup> <sup>134</sup> <sup>135</sup> <sup>136</sup> <sup>137</sup> <sup>138</sup> <sup>139</sup> <sup>140</sup> <sup>141</sup> <sup>142</sup> <sup>143</sup> <sup>144</sup> <sup>145</sup> <sup>146</sup> <sup>147</sup> <sup>148</sup> <sup>149</sup> <sup>150</sup> <sup>151</sup> <sup>152</sup> <sup>153</sup> <sup>154</sup> <sup>155</sup> <sup>156</sup> <sup>157</sup> <sup>158</sup> <sup>159</sup> <sup>160</sup> <sup>161</sup> <sup>162</sup> <sup>163</sup> <sup>164</sup> <sup>165</sup> <sup>166</sup> <sup>167</sup> <sup>168</sup> <sup>169</sup> <sup>170</sup> <sup>171</sup> <sup>172</sup> <sup>173</sup> <sup>174</sup> <sup>175</sup> <sup>176</sup> <sup>177</sup> <sup>178</sup> <sup>179</sup> <sup>180</sup> <sup>181</sup> <sup>182</sup> <sup>183</sup> <sup>184</sup> <sup>185</sup> <sup>186</sup> <sup>187</sup> <sup>188</sup> <sup>189</sup> <sup>190</sup> <sup>191</sup> <sup>192</sup> <sup>193</sup> <sup>194</sup> <sup>195</sup> <sup>196</sup> <sup>197</sup> <sup>198</sup> <sup>199</sup> <sup>200</sup> <sup>201</sup> <sup>202</sup> <sup>203</sup> <sup>204</sup> <sup>205</sup> <sup>206</sup> <sup>207</sup> <sup>208</sup> <sup>209</sup> <sup>210</sup> <sup>211</sup> <sup>212</sup> <sup>213</sup> <sup>214</sup> <sup>215</sup> <sup>216</sup> <sup>217</sup> <sup>218</sup> <sup>219</sup> <sup>220</sup> <sup>221</sup> <sup>222</sup> <sup>223</sup> <sup>224</sup> <sup>225</sup> <sup>226</sup> <sup>227</sup> <sup>228</sup> <sup>229</sup> <sup>230</sup> <sup>231</sup> <sup>232</sup> <sup>233</sup> <sup>234</sup> <sup>235</sup> <sup>236</sup> <sup>237</sup> <sup>238</sup> <sup>239</sup> <sup>240</sup> <sup>241</sup> <sup>242</sup> <sup>243</sup> <sup>244</sup> <sup>245</sup> <sup>246</sup> <sup>247</sup> <sup>248</sup> <sup>249</sup> <sup>250</sup> <sup>251</sup> <sup>252</sup> <sup>253</sup> <sup>254</sup> <sup>255</sup> <sup>256</sup> <sup>257</sup> <sup>258</sup> <sup>259</sup> <sup>260</sup> <sup>261</sup> <sup>262</sup> <sup>263</sup> <sup>264</sup> <sup>265</sup> <sup>266</sup> <sup>267</sup> <sup>268</sup> <sup>269</sup> <sup>270</sup> <sup>271</sup> <sup>272</sup> <sup>273</sup> <sup>274</sup> <sup>275</sup> <sup>276</sup> <sup>277</sup> <sup>278</sup> <sup>279</sup> <sup>280</sup> <sup>281</sup> <sup>282</sup> <sup>283</sup> <sup>284</sup> <sup>285</sup> <sup>286</sup> <sup>287</sup> <sup>288</sup> <sup>289</sup> <sup>290</sup> <sup>291</sup> <sup>292</sup> <sup>293</sup> <sup>294</sup> <sup>295</sup> <sup>296</sup> <sup>297</sup> <sup>298</sup> <sup>299</sup> <sup>300</sup> <sup>301</sup> <sup>302</sup> <sup>303</sup> <sup>304</sup> <sup>305</sup> <sup>306</sup> <sup>307</sup> <sup>308</sup> <sup>309</sup> <sup>310</sup> <sup>311</sup> <sup>312</sup> <sup>313</sup> <sup>314</sup> <sup>315</sup> <sup>316</sup> <sup>317</sup> <sup>318</sup> <sup>319</sup> <sup>320</sup> <sup>321</sup> <sup>322</sup> <sup>323</sup> <sup>324</sup> <sup>325</sup> <sup>326</sup> <sup>327</sup> <sup>328</sup> <sup>329</sup> <sup>330</sup> <sup>331</sup> <sup>332</sup> <sup>333</sup> <sup>334</sup> <sup>335</sup> <sup>336</sup> <sup>337</sup> <sup>338</sup> <sup>339</sup> <sup>340</sup> <sup>341</sup> <sup>342</sup> <sup>343</sup> <sup>344</sup> <sup>345</sup> <sup>346</sup> <sup>347</sup> <sup>348</sup> <sup>349</sup> <sup>350</sup> <sup>351</sup> <sup>352</sup> <sup>353</sup> <sup>354</sup> <sup>355</sup> <sup>356</sup> <sup>357</sup> <sup>358</sup> <sup>359</sup> <sup>360</sup> <sup>361</sup> <sup>362</sup> <sup>363</sup> <sup>364</sup> <sup>365</sup> <sup>366</sup> <sup>367</sup> <sup>368</sup> <sup>369</sup> <sup>370</sup> <sup>371</sup> <sup>372</sup> <sup>373</sup> <sup>374</sup> <sup>375</sup> <sup>376</sup> <sup>377</sup> <sup>378</sup> <sup>379</sup> <sup>380</sup> <sup>381</sup> <sup>382</sup> <sup>383</sup> <sup>384</sup> <sup>385</sup> <sup>386</sup> <sup>387</sup> <sup>388</sup> <sup>389</sup> <sup>390</sup> <sup>391</sup> <sup>392</sup> <sup>393</sup> <sup>394</sup> <sup>395</sup> <sup>396</sup> <sup>397</sup> <sup>398</sup> <sup>399</sup> <sup>400</sup> <sup>401</sup> <sup>402</sup> <sup>403</sup> <sup>404</sup> <sup>405</sup> <sup>406</sup> <sup>407</sup> <sup>408</sup> <sup>409</sup> <sup>410</sup> <sup>411</sup> <sup>412</sup> <sup>413</sup> <sup>414</sup> <sup>415</sup> <sup>416</sup> <sup>417</sup> <sup>418</sup> <sup>419</sup> <sup>420</sup> <sup>421</sup> <sup>422</sup> <sup>423</sup> <sup>424</sup> <sup>425</sup> <sup>426</sup> <sup>427</sup> <sup>428</sup> <sup>429</sup> <sup>430</sup> <sup>431</sup> <sup>432</sup> <sup>433</sup> <sup>434</sup> <sup>435</sup> <sup>436</sup> <sup>437</sup> <sup>438</sup> <sup>439</sup> <sup>440</sup> <sup>441</sup> <sup>442</sup> <sup>443</sup> <sup>444</sup> <sup>445</sup> <sup>446</sup> <sup>447</sup> <sup>448</sup> <sup>449</sup> <sup>450</sup> <sup>451</sup> <sup>452</sup> <sup>453</sup> <sup>454</sup> <sup>455</sup> <sup>456</sup> <sup>457</sup> <sup>458</sup> <sup>459</sup> <sup>460</sup> <sup>461</sup> <sup>462</sup> <sup>463</sup> <sup>464</sup> <sup>465</sup> <sup>466</sup> <sup>467</sup> <sup>468</sup> <sup>469</sup> <sup>470</sup> <sup>471</sup> <sup>472</sup> <sup>473</sup> <sup>474</sup> <sup>475</sup> <sup>476</sup> <sup>477</sup> <sup>478</sup> <sup>479</sup> <sup>480</sup> <sup>481</sup> <sup>482</sup> <sup>483</sup> <sup>484</sup> <sup>485</sup> <sup>486</sup> <sup>487</sup> <sup>488</sup> <sup>489</sup> <sup>490</sup> <sup>491</sup> <sup>492</sup> <sup>493</sup> <sup>494</sup> <sup>495</sup> <sup>496</sup> <sup>497</sup> <sup>498</sup> <sup>499</sup> <sup>500</sup> <sup>501</sup> <sup>502</sup> <sup>503</sup> <sup>504</sup> <sup>505</sup> <sup>506</sup> <sup>507</sup> <sup>508</sup> <sup>509</sup> <sup>510</sup> <sup>511</sup> <sup>512</sup> <sup>513</sup> <sup>514</sup> <sup>515</sup> <sup>516</sup> <sup>517</sup> <sup>518</sup> <sup>519</sup> <sup>520</sup> <sup>521</sup> <sup>522</sup> <sup>523</sup> <sup>524</sup> <sup>525</sup> <sup>526</sup> <sup>527</sup> <sup>528</sup> <sup>529</sup> <sup>530</sup> <sup>531</sup> <sup>532</sup> <sup>533</sup> <sup>534</sup> <sup>535</sup> <sup>536</sup> <sup>537</sup> <sup>538</sup> <sup>539</sup> <sup>540</sup> <sup>541</sup> <sup>542</sup> <sup>543</sup> <sup>544</sup> <sup>545</sup> <sup>546</sup> <sup>547</sup> <sup>548</sup> <sup>549</sup> <sup>550</sup> <sup>551</sup> <sup>552</sup> <sup>553</sup> <sup>554</sup> <sup>555</sup> <sup>556</sup> <sup>557</sup> <sup>558</sup> <sup>559</sup> <sup>560</sup> <sup>561</sup> <sup>562</sup> <sup>563</sup> <sup>564</sup> <sup>565</sup> <sup>566</sup> <sup>567</sup> <sup>568</sup> <sup>569</sup> <sup>570</sup> <sup>571</sup> <sup>572</sup> <sup>573</sup> <sup>574</sup> <sup>575</sup> <sup>576</sup> <sup>577</sup> <sup>578</sup> <sup>579</sup> <sup>580</sup> <sup>581</sup> <sup>582</sup> <sup>583</sup> <sup>584</sup> <sup>585</sup> <sup>586</sup> <sup>587</sup> <sup>588</sup> <sup>589</sup> <sup>590</sup> <sup>591</sup> <sup>592</sup> <sup>593</sup> <sup>594</sup> <sup>595</sup> <sup>596</sup> <sup>597</sup> <sup>598</sup> <sup>599</sup> <sup>600</sup> <sup>601</sup> <sup>602</sup> <sup>603</sup> <sup>604</sup> <sup>605</sup> <sup>606</sup> <sup>607</sup> <sup>608</sup> <sup>609</sup> <sup>610</sup> <sup>611</sup> <sup>612</sup> <sup>613</sup> <sup>614</sup> <sup>615</sup> <sup>616</sup> <sup>617</sup> <sup>618</sup> <sup>619</sup> <sup>620</sup> <sup>621</sup> <sup>622</sup> <sup>623</sup> <sup>624</sup> <sup>625</sup> <sup>626</sup> <sup>627</sup> <sup>628</sup> <sup>629</sup> <sup>630</sup> <sup>631</sup> <sup>632</sup> <sup>633</sup> <sup>634</sup> <sup>635</sup> <sup>636</sup> <sup>637</sup> <sup>638</sup> <sup>639</sup> <sup>640</sup> <sup>641</sup> <sup>642</sup> <sup>643</sup> <sup>644</sup> <sup>645</sup> <sup>646</sup> <sup>647</sup> <sup>648</sup> <sup>649</sup> <sup>650</sup> <sup>651</sup> <sup>652</sup> <sup>653</sup> <sup>654</sup> <sup>655</sup> <sup>656</sup> <sup>657</sup> <sup>658</sup> <sup>659</sup> <sup>660</sup> <sup>661</sup> <sup>662</sup> <sup>663</sup> <sup>664</sup> <sup>665</sup> <sup>666</sup> <sup>667</sup> <sup>668</sup> <sup>669</sup> <sup>670</sup> <sup>671</sup> <sup>672</sup> <sup>673</sup> <sup>674</sup> <sup>675</sup> <sup>676</sup> <sup>677</sup> <sup>678</sup> <sup>679</sup> <sup>680</sup> <sup>681</sup> <sup>682</sup> <sup>683</sup> <sup>684</sup> <sup>685</sup> <sup>686</sup> <sup>687</sup> <sup>688</sup> <sup>689</sup> <sup>690</sup> <sup>691</sup> <sup>692</sup> <sup>693</sup> <sup>694</sup> <sup>695</sup> <sup>696</sup> <sup>697</sup> <sup>698</sup> <sup>699</sup> <sup>700</sup> <sup>701</sup> <sup>702</sup> <sup>703</sup> <sup>704</sup> <sup>705</sup> <sup>706</sup> <sup>707</sup> <sup>708</sup> <sup>709</sup> <sup>710</sup> <sup>711</sup> <sup>712</sup> <sup>713</sup> <sup>714</sup> <sup>715</sup> <sup>716</sup> <sup>717</sup> <sup>718</sup> <sup>719</sup> <sup>720</sup> <sup>721</sup> <sup>722</sup> <sup>723</sup> <sup>724</sup> <sup>725</sup> <sup>726</sup> <sup>727</sup> <sup>728</sup> <sup>729</sup> <sup>730</sup> <sup>731</sup> <sup>732</sup> <sup>733</sup> <sup>734</sup> <sup>735</sup> <sup>736</sup> <sup>737</sup> <sup>738</sup> <sup>739</sup> <sup>740</sup> <sup>741</sup> <sup>742</sup> <sup>743</sup> <sup>744</sup> <sup>745</sup> <sup>746</sup> <sup>747</sup> <sup>748</sup> <sup>749</sup> <sup>750</sup> <sup>751</sup> <sup>752</sup> <sup>753</sup> <sup>754</sup> <sup>755</sup> <sup>756</sup> <sup>757</sup> <sup>758</sup> <sup>759</sup> <sup>760</sup> <sup>761</sup> <sup>762</sup> <sup>763</sup> <sup>764</sup> <sup>765</sup> <sup>766</sup> <sup>767</sup> <sup>768</sup> <sup>769</sup> <sup>770</sup> <sup>771</sup> <sup>772</sup> <sup>773</sup> <sup>774</sup> <sup>775</sup> <sup>776</sup> <sup>777</sup> <sup>778</sup> <sup>779</sup> <sup>780</sup> <sup>781</sup> <sup>782</sup> <sup>783</sup> <sup>784</sup> <sup>785</sup> <sup>786</sup> <sup>787</sup> <sup>788</sup> <sup>789</sup> <sup>790</sup> <sup>791</sup> <sup>792</sup> <sup>793</sup> <sup>794</sup> <sup>795</sup> <sup>796</sup> <sup>797</sup> <sup>798</sup> <sup>799</sup> <sup>800</sup> <sup>801</sup> <sup>802</sup> <sup>803</sup> <sup>804</sup> <sup>805</sup> <sup>806</sup> <sup>807</sup> <sup>808</sup> <sup>809</sup> <sup>810</sup> <sup>811</sup> <sup>812</sup> <sup>813</sup> <sup>814</sup> <sup>815</sup> <sup>816</sup> <sup>817</sup> <sup>818</sup> <sup>819</sup> <sup>820</sup> <sup>821</sup> <sup>822</sup> <sup>823</sup> <sup>824</sup> <sup>825</sup> <sup>826</sup> <sup>827</sup> <sup>828</sup> <sup>829</sup> <sup>830</sup> <sup>831</sup> <sup>832</sup> <sup>833</sup> <sup>834</sup> <sup>835</sup> <sup>836</sup> <sup>837</sup> <sup>838</sup> <sup>839</sup> <sup>840</sup> <sup>841</sup> <sup>842</sup> <sup>843</sup> <sup>844</sup> <sup>845</sup> <sup>846</sup> <sup>847</sup> <sup>848</sup> <sup>849</sup> <sup>850</sup> <sup>851</sup> <sup>852</sup> <sup>853</sup> <sup>854</sup> <sup>855</sup> <sup>856</sup> <sup>857</sup> <sup>858</sup> <sup>859</sup> <sup>860</sup> <sup>861</sup> <sup>862</sup> <sup>863</sup> <sup>864</sup> <sup>865</sup> <sup>866</sup> <sup>867</sup> <sup>868</sup> <sup>869</sup> <sup>870</sup> <sup>871</sup> <sup>872</sup> <sup>873</sup> <sup>874</sup> <sup>875</sup> <sup>876</sup> <sup>877</sup> <sup>878</sup> <sup>879</sup> <sup>880</sup> <sup>881</sup> <sup>882</sup> <sup>883</sup> <sup>884</sup> <sup>885</sup> <sup>886</sup> <sup>887</sup> <sup>888</sup> <sup>889</sup> <sup>890</sup> <sup>891</sup> <sup>892</sup> <sup>893</sup> <sup>894</sup> <sup>895</sup> <sup>896</sup> <sup>897</sup> <sup>898</sup> <sup>899</sup> <sup>900</sup> <sup>901</sup> <sup>902</sup> <sup>903</sup> <sup>904</sup> <sup>905</sup> <sup>906</sup> <sup>907</sup> <sup>908</sup> <sup>909</sup> <sup>910</sup> <sup>911</sup> <sup>912</sup> <sup>913</sup> <sup>914</sup> <sup>915</sup> <sup>916</sup> <sup>917</sup> <sup>918</sup> <sup>919</sup> <sup>920</sup> <sup>921</sup> <sup>922</sup> <sup>923</sup> <sup>924</sup> <sup>925</sup> <sup>926</sup> <sup>927</sup> <sup>928</sup> <sup>929</sup> <sup>930</sup> <sup>931</sup> <sup>932</sup> <sup>933</sup> <sup>934</sup> <sup>935</sup> <sup>936</sup> <sup>937</sup> <sup>938</sup> <sup>939</sup> <sup>940</sup> <sup>941</sup> <sup>942</sup> <sup>943</sup> <sup>944</sup> <sup>945</sup> <sup>946</sup> <sup>947</sup> <sup>948</sup> <sup>949</sup> <sup>950</sup> <sup>951</sup> <sup>952</sup> <sup>953</sup> <sup>954</sup> <sup>955</sup> <sup>956</sup> <sup>957</sup> <sup>958</sup> <sup>959</sup> <sup>960</sup> <sup>961</sup> <sup>962</sup> <sup>963</sup> <sup>964</sup> <sup>965</sup> <sup>966</sup> <sup>967</sup> <sup>968</sup> <sup>969</sup> <sup>970</sup> <sup>971</sup> <sup>972</sup> <sup>973</sup> <sup>974</sup> <sup>975</sup> <sup>976</sup> <sup>977</sup> <sup>978</sup> <sup>979</sup> <sup>980</sup> <sup>981</sup> <sup>982</sup> <sup>983</sup> <sup>984</sup> <sup>985</sup> <sup>986</sup> <sup>987</sup> <sup>988</sup> <sup>989</sup> <sup>990</sup> <sup>991</sup> <sup>992</sup> <sup>993</sup> <sup>994</sup> <sup>995</sup> <sup>996</sup> <sup>997</sup> <sup>998</sup> <sup>999</sup> <sup>1000</sup> <sup>1001</sup> <sup>1002</sup> <sup>1003</sup> <sup>1004</sup> <sup>1005</sup> <sup>1006</sup> <sup>1007</sup> <sup>1008</sup> <sup>1009</sup> <sup>1010</sup> <sup>1011</sup> <sup>1012</sup> <sup>1013</sup> <sup>1014</sup> <sup>1015</sup> <sup>1016</sup> <sup>1017</sup> <sup>1018</sup> <sup>1019</sup> <sup>1020</sup> <sup>1021</sup> <sup>1022</sup> <sup>1023</sup> <sup>1024</sup> <sup>1025</sup> <sup>1026</sup> <sup>1027</sup> <sup>1028</sup> <sup>1029</sup> <sup>1030</sup> <sup>1031</sup> <sup>1032</sup> <sup>1033</sup> <sup>1034</sup> <sup>1035</sup> <sup>1036</sup> <sup>1037</sup> <sup>1038</sup> <sup>1039</sup> <sup>1040</sup> <sup>1041</sup> <sup>1042</sup> <sup>1043</sup> <sup>1044</sup> <sup>1045</sup> <sup>1046</sup> <sup>1047</sup> <sup>1048</sup> <sup>1049</sup> <sup>1050</sup> <sup>1051</sup> <sup>1052</sup> <sup>1053</sup> <sup>1054</sup> <sup>1055</sup> <sup>1056</sup> <sup>1057</sup> <sup>1058</sup> <sup>1059</sup> <sup>1060</sup> <sup>1061</sup> <sup>1062</sup> <sup>1063</sup> <sup>1064</sup> <sup>1065</sup> <sup>1066</sup> <sup>1067</sup> <sup>1068</sup> <sup>1069</sup> <sup>1070</sup> <sup>1071</sup> <sup>1072</sup> <sup>1073</sup> <sup>1074</sup> <sup>1075</sup> <sup>1076</sup> <sup>1077</sup> <sup>1078</sup> <sup>1079</sup> <sup>1080</sup> <sup>1081</sup> <sup>1082</sup> <sup>1083</sup> <sup>1084</sup> <sup>1085</sup> <sup>1086</sup> <sup>1087</sup> <sup>1088</sup> <sup>1089</sup> <sup>1090</sup> <sup>1091</sup> <sup>1092</sup> <sup>1093</sup> <sup>1094</sup> <sup>1095</sup> <sup>1096</sup> <sup>1097</sup> <sup>1098</sup> <sup>1099</sup> <sup>1100</sup> <sup>1101</sup> <sup>1102</sup> <sup>1103</sup> <sup>1104</sup> <sup>1105</sup> <sup>1106</sup> <sup>1107</sup> <sup>1108</sup> <sup>1109</sup> <sup>1110</sup> <sup>1111</sup> <sup>1112</sup> <sup>1113</sup> <sup>1114</sup> <sup>1115</sup> <sup>1116</sup> <sup>1117</sup> <sup>1118</sup> <sup>1119</sup> <sup>1120</sup> <sup>1121</sup> <sup>1122</sup> <sup>1123</sup> <sup>1124</sup> <sup>1125</sup> <sup>1126</sup> <sup>1127</sup> <sup>1128</sup> <sup>1129</sup> <sup>1130</sup> <sup>1131</sup> <sup>1132</sup> <sup>1133</sup> <sup>1134</sup> <sup>1135</sup> <sup>1136</sup> <sup>1137</sup> <sup>1138</sup> <sup>1139</sup> <sup>1140</sup> <sup>1141</sup> <sup>1142</sup> <sup>1143</sup> <sup>1144</sup> <sup>1145</sup> <sup>1146</sup> <sup>1147</sup> <sup>1148</sup> <sup>1149</sup> <sup>1150</sup> <sup>1151</sup> <sup>1152</sup> <sup>1153</sup> <sup>1154</sup> <sup>1155</sup> <sup>1156</sup> <sup>1157</sup> <sup>1158</sup> <sup>1159</sup> <sup>1160</sup> <sup>1161</sup> <sup>1162</sup> <sup>1163</sup> <sup>1164</sup> <sup>1165</sup> <sup>1166</sup> <sup>1167</sup> <sup>1168</sup> <sup>1169</sup> <sup>1170</sup> <sup>1171</sup> <sup>1172</sup> <sup>1173</sup> <sup>1174</sup> <sup>1175</sup> <sup>1176</sup> <sup>1177</sup> <sup>1178</sup> <sup>1179</sup> <sup>1180</sup> <sup>1181</sup> <sup>1182</sup> <sup>1183</sup> <sup>1184</sup> <sup>1185</sup> <sup>1186</sup> <sup>1187</sup> <sup>1188</sup> <sup>1189</sup> <sup>1190</sup> <sup>1191</sup> <sup>1192</sup> <sup>1193</sup> <sup>1194</sup> <sup>1195</sup> <sup>1196</sup> <sup>1197</sup> <sup>1198</sup> <sup>1199</sup> <sup>1200</sup> <sup>1201</sup> <sup>1202</sup> <sup>1203</sup> <sup>1204</sup> <sup>1205</sup> <sup>1206</sup> <sup>1207</sup> <sup>1208</sup> <sup>1209</sup> <sup>1210</sup> <sup>1211</sup> <sup>1212</sup> <sup>1213</sup> <sup>1214</sup> <sup>1215</sup> <sup>1216</sup> <sup>1217</sup> <sup>1218</sup> <sup>1219</sup> <sup>1220</sup> <sup>1221</sup> <sup>1222</sup> <sup>1223</sup> <sup>1224</sup> <sup>1225</sup> <sup>1226</sup> <sup>1227</sup> <sup>1228</sup> <sup>1229</sup> <sup>1230</sup> <sup>1231</sup> <sup>1232</sup> <sup>1233</sup> <sup>1234</sup> <sup>1235</sup> <sup>1236</sup> <sup>1237</sup> <sup>1238</sup> <sup>1239</sup> <sup>1240</sup> <sup>1241</sup> <sup>1242</sup> <sup>1243</sup> <sup>1244</sup> <sup>1245</sup> <sup>1246</sup> <sup>1247</sup> <sup>1248</sup> <sup>1249</sup> <sup>1250</sup> <sup>1251</sup> <sup>1252</sup> <sup>1253</sup> <sup>1254</sup> <sup>1255</sup> <sup>1256</sup> <sup>1257</sup> <sup>1258</sup> <sup>1259</sup> <sup>1260</sup> <sup>1261</sup> <sup>1262</sup> <sup>1263</sup> <sup>1264</sup> <sup>1265</sup> <sup>1266</sup> <sup>1267</sup> <sup>1268</sup> <sup>1269</sup> <sup>1270</sup> <sup>1271</sup> <sup>1272</sup> <sup>1273</sup> <sup>1274</sup> <sup>1275</sup> <sup>1276</sup> <sup>1277</sup> <sup>1278</sup> <sup>1279</sup> <sup>1280</sup> <sup>1281</sup> <sup>1282</</sup>

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTE-MORTEM AND POST-MORTEM RECORDS AS USED  
IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

### CASE 28071

#### PRESENTATION OF CASE

A forty-five-year-old housewife was admitted to the hospital because of profuse vaginal bleeding of eight hours' duration, following a long course of menstrual irregularity.

Following the menarche, at twelve years, the menses were quite profuse. At the age of twenty-one, the patient received three radium treatments in another hospital, following which the menses stopped for six weeks. At the age of about thirty, a "tube and ovary" were removed at the other hospital, and another course of radium therapy was given. In the seven years following this, the menses were absent, and the patient experienced hot flashes. The menses then returned, and were regular, although scanty. Following the last regular period, one year before entry, there was amenorrhea lasting seven months. There was then slight, continuous bleeding for two months, stopping two days before entry. Following a strenuous evening, the patient was aroused early in the morning by profuse vaginal bleeding, with the passage of large clots. Throughout the course of the illness, there were no other symptoms until the last episode of vigorous bleeding, when there was some cramping. The patient had been married for seven years but had never been pregnant.

The family history was irrelevant. Appendectomy and cholecystectomy had been performed some years previously.

On admission, the patient appeared well developed and nourished. The chest and upper abdomen were normal. There was moderate suprapubic tenderness, with slight resistance to palpation. There was some suggestion of a pelvic mass. However, deep palpation and vaginal examination were omitted because of the recent bleeding. Four well-healed scars of previous abdominal operations were present.

The temperature was 100°F., the pulse 100, and the respirations 20. The blood pressure was 120 systolic, 90 diastolic.

Examination of the blood showed a red-cell count of 4,730,000 with 14.3 gm. hemoglobin. The blood Hinton reaction was negative. The urine was normal.

On the fifth hospital day, an operation was performed.

#### DIFFERENTIAL DIAGNOSIS

DR. MARSHALL K. BARTLETT: When we look over the history, there are several interesting points and several things that we should like to know. I assume that the periods from the age of twelve up to twenty-one, although profuse, were regular. There is no such statement, but irregularity is a point significant enough to have been mentioned if present.

The next interesting thing is that the patient was given three radium treatments at the age of twenty-one,—in other words, twenty-four years previous to entry,—following which she had no periods for six weeks; then, at about thirty, or fifteen years before entry, she had a tube and an ovary removed and another course of radium. This was followed by a longer period of amenorrhea, lasting seven months, during which she had hot flashes. Then, the menstrual periods returned, being regular although scanty until a year before entry, when they stopped. It would be interesting to know whether the patient had hot flashes during the time she was having those periods and during the last period of amenorrhea; the arithmetic does not come out right, to my way of thinking. She is said to have had the last period one year before entry, but amenorrhea for seven months and flowing for two months, stopping two days before entry, add up to only nine months. That is a minor point, but if one wanted to consider the possibility of pregnancy, the slight difference might be important. It is interesting that the last flow was continuous, whereas previously she had always had regular cycles.

What are the possible causes for this? I think that even on the basis of this meager physical examination it is possible to rule out a full-term pregnancy, and from the dates it would have to be full term. Was this a dysfunctional type of flow associated with endocrine imbalance? Certainly, there is a good background, with all the menstrual difficulty that is reported. Could the bleeding have been due to a polyp of the cervix or one of the endometrium? I think that the profuse bleeding just before entry would be unusual for cervical polyp, although possible, and that it could be associated with an endometrial polyp.

Could it be associated with the presence of fibroids? It could, and I see no way to rule it out on the basis of this information. The same thing applies to a benign ovarian cyst, if one was present. I do not see how one can be sure. Of these benign conditions, it seems to me that the

most probable one is the dysfunctional type of flow based on endocrine imbalance.

What could we say in favor of a malignant cause? Two points rather favor that. In the first place, the patient had had two courses of radium treatment a number of years before entry, which raises at least a theoretical possibility that she might have developed a malignant neoplasm on the basis of previous radiation. The other thing is the bleeding, which was different in type from what she had had before. It was continuous rather than intermittent. Could this have come from a carcinoma of the cervix? I believe that it could. Certainly, a carcinoma of the cervix can occasionally cause a sudden profuse hemorrhage. It is not common, but we do see it. Could it have been a carcinoma of the endometrium? I should think that it could, and if we give any weight to the previous radiation, the endometrium would be the logical place to look for it. The fact that the patient had cramps with the last episode that brought her to the hospital suggests something inside the uterus. How about a malignant ovarian cyst? Certainly, that can give slight continuous bleeding for two months. I think it would be unlikely to give profuse hemorrhage such as she had just before she came in. Could it have been a carcinoma of the tube? We know that that gives slight bleeding, with intermittent gushes, but I do not believe it would give a profuse type of hemorrhage.

We have all these possibilities, and I do not see that we have very much to go on in choosing between them. The points we have to work on are fairly small ones, but we must make a choice. It seems to me an even choice between a benign type of dysfunctional bleeding and bleeding on a malignant basis. Of the two, I am a little inclined to think that it was probably on a malignant basis, and of the various possible sites of carcinoma, the endometrium is probably the most logical choice.

DR. JACOB LERMAN: Could the patient have been radiated because they found a malignant ovary or something else at the time? Why was she given radium?

DR. BARTLETT: I should think that she was given small doses of radium to control the bleeding. If the ovary had proved to be malignant, it would have been more reasonable to go back and do a hysterectomy, with removal of the other tube and ovary as well.

#### CLINICAL DIAGNOSES

Functional uterine bleeding.  
Endometrial polyp.

#### DR. BARTLETT'S DIAGNOSIS

Carcinoma of endometrium.

#### ANATOMICAL DIAGNOSIS

Carcinoma of endometrium.

#### PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: The patient was examined vaginally under anesthesia. A normal cervix was found. The uterus was curetted, and a considerable amount of polypoid material, which grossly did not look malignant, was removed, but a frozen section showed that it was carcinoma. The curettage was then followed up by a complete hysterectomy, and a carcinoma of the fundus was found of quite undifferentiated character and a rather high degree of malignancy.

DR. LANGDON S. PARSONS: How much did the uterine radiation have to do with this?

DR. MALLORY: There is no way of telling. The one remaining ovary showed a single cyst, but was otherwise negative. The uterus was still quite small. There was no obvious extension of the tumor into the pelvis. It was not possible to feel the liver for metastases, because of adhesions of the omentum secondary to the previous operations, but at the end of the operation it seemed that a favorable result might be expected.

#### CASE 28072

#### PRESENTATION OF CASE

*First admission.* A forty-seven-year-old plumber was admitted to the hospital complaining of steady abdominal pain of twenty hours' duration.

The patient was fairly well until two years before admission, when he first noticed a steady, aching, low substernal pain and feeling of compression, which had persisted almost constantly since that time. The discomfort was usually worse at night and was sometimes relieved if the patient walked the floor. It was never severe enough to keep him awake, and was not influenced by exertion, breathing or swallowing. At approximately the same time, he began having dull headaches, became weak and tired, and developed nocturia (once). He entered an outside hospital for a checkup, and was told that his blood pressure was "276." After discharge, he continued to work, and was fairly well until twenty hours before admission, when while eating a sandwich and drinking coffee at 10 p.m., he was suddenly seized with a severe steady pain beneath the xiphoid; this soon radiated through to the back and up between the shoulder blades. He felt nauseated and vomited

a small amount of food. The pain increased in severity, and half an hour after its onset he attempted to "walk it off." He then experienced a severe cramp in the back of the right leg, which remained until he stopped walking. It failed to return, thereafter, but the subxiphoid epigastric pain continued in spite of two hypodermic injections given by his physician. He finally fell asleep about 4 a.m., but was awakened at 7 a.m. by the same pain. Throughout the morning and afternoon before admission, the pain continued while he restlessly paced the floor.

Physical examination revealed a well-developed and well-nourished man who was walking restlessly in acute distress because of severe, steady epigastric pain. He was unable to lie flat on his back, writhing constantly. He felt somewhat better lying on his side, sitting or standing erect. There was no sweating, pallor or cyanosis. The fundi showed "moderate arteriosclerosis." The teeth were carious. The lungs were clear and resonant throughout. The heart was slightly enlarged to the left, the pulse full, 85 per minute, and regular. There was a faint systolic murmur at the apex. The aortic second sound was louder than the pulmonic. The sounds were of good quality. No friction rub was heard. There was marked tenderness, without spasm, high in the midepigastrium, but there were no masses or palpable viscera, and no tympany or abnormal peristalsis. No other positive findings were elicited.

The temperature was 99.8°F., the pulse 85, and the respirations 20. The blood pressure was 180 systolic, 110 diastolic.

Examination of the blood showed a red-cell count of 4,500,000 with 100 per cent hemoglobin, and a white-cell count of 14,300 with 90 per cent polymorphonuclears. The urine and stools were normal. The phenolsulfonphthalein urinary-excretion test showed 25 per cent excretion in fifteen minutes and 60 per cent in one hour. The sedimentation rate ranged between 0.7 and 0.8 mm. per minute. The serum nonprotein nitrogen was 21 mg. per 100 cc. The blood Hinton reaction was negative. An electrocardiogram showed a ventricular rate of 80, with normal rhythm, a PR interval of 0.19 second, diphasic T<sub>1</sub>, low T<sub>2</sub> and late inversion of T<sub>4</sub>, with left-axis deviation. Roentgenograms of the abdomen with the patient lying down showed one loop of slightly dilated, air-filled small intestine in the left upper quadrant. There was an area of poorly defined decreased density overlying and extending to both sides of the fourth lumbar vertebra. Films in the upright position showed no evidence of free air below the diaphragm. The psoas shadows were clearly

outlined. Films of the gall-bladder region with Graham test showed no gallstone. Chest films, both anteroposterior and lateral, revealed a markedly tortuous aorta. Intravenous pyelograms nineteen days after admission showed that there was prompt excretion of poorly concentrated dye on both sides, but the concentration on the right side was not sufficient to outline the kidney pelvis. There were no air-filled dilated loops of bowel. A gastrointestinal series was negative.

For the first four hospital days, the patient ran a slightly elevated temperature (100 to 101°F.), pulse (90 to 95) and respirations (22 to 25), but for the remaining five weeks his chart was flat. The abdominal pain persisted for six days, required heavy morphinization, and then gradually decreased. In this interim, its main focus migrated somewhat from the midepigastrium to the right upper quadrant, and then, as it slowly disappeared, to both lower quadrants. The blood pressures in the arms and legs were about equal at 180 systolic, 100 diastolic. On the fourth and fifth days of the illness, the urine contained 40 and 20 red blood cells per high-power field in the sediment, respectively; thereafter, it was normal. The electrocardiogram on the second hospital day showed low T<sub>1</sub>, T<sub>3</sub> and T<sub>4</sub>, with slight left-axis deviation, and on the fifth day, low T<sub>1</sub>, with a late inversion of T<sub>4</sub>. Convalescence was uneventful, and the patient was discharged on the forty-first hospital day.

*Second admission* (two and a half months later). Following discharge, the patient remained at home on a careful rest regime for six weeks. He then began doing light work, and seemed well until one week before admission, when substernal pain and a sense of chest constriction reappeared, apparently unrelated to exertion, but relieved within half an hour by nitroglycerin.

Physical examination was unchanged from that on the first entry, except that the heart was enlarged 2 cm. beyond the midclavicular line and the blood pressure was 220 systolic, 140 diastolic, in all extremities. The temperature, pulse and respirations were normal. Both urine and blood examinations were negative except for a slightly elevated white-cell count, ranging from 8000 to 13,000. The electrocardiograms were essentially unchanged, but a review of the x-ray films of the chest showed a definite dilatation of the aortic arch when compared with films taken two years previously in the Out Patient Department.

While in the hospital, the patient had a severe one-and-a-half-hour attack of chest pain, which radiated down the left arm and was only partially relieved by morphine. The left radial pulse

was definitely weaker than the right, and the blood pressure, in the right arm was 170 systolic, 120 diastolic, whereas that in the left was 120 systolic, 80 diastolic. There were no residual symptoms following this episode. The next day, the blood pressures in the extremities were about equal at 210 to 240 systolic, 150 to 180 diastolic. The patient was discharged on the twenty-fourth hospital day.

*Third admission* (nine months later). Following discharge, the patient had been well, using nitroglycerin occasionally for chest pain. He had rested for six months, after which he had been doing sedentary work. Twenty-four hours before entry, while working, he experienced the rapid onset of severe pain in the left arm, with an associated mild oppression in the upper sternum and pain on both sides of the neck. This lasted one hour, and one hour later it reappeared. He took a nitroglycerin pill without benefit, and the next day entered the hospital, where an electrocardiogram showed a ventricular rate of 80, with normal rhythm, T<sub>1</sub> inverted, T<sub>2</sub> diphasic, T<sub>3</sub> upright, T<sub>4</sub> inverted, R<sub>4</sub> present and moderate left-axis deviation. Five days later, T<sub>2</sub> was inverted, T<sub>4</sub> more deeply inverted, and T<sub>1</sub> slightly more so. Funduscopic observations revealed several fresh hemorrhages in both fundi. The physical and laboratory findings were otherwise unchanged. The patient remained in the hospital for eight days, during which his chart was normal.

*Final admission* (four months later). Eight hours before admission, the patient had a sudden attack of substernal pain radiating down both arms and into the neck, following the ingestion of two glasses of beer. On examination, he was in obvious pain, breathing rapidly and groaning from time to time. There were a few crackles at the left base posteriorly. The heart sounds were distant and not of good quality; the pulmonary and aortic second sounds were equal. The blood pressure was 194 systolic, 118 diastolic. An electrocardiogram showed no essential change from the last, except biphasic instead of inverted T<sub>1</sub> and T<sub>2</sub>. The white-cell count was 15,000. The electrocardiogram two days later showed no change. The patient developed a gallop rhythm, a fall in systolic blood pressure to 158, pallor, sweating and cold extremities, and showed crepitant rales and wheezes at both lung bases, an enlarged slightly tender liver, without edema of the sacrum or the extremities, and distention of the neck veins. He was given oxygen and morphine, and was digitalized. On the third hospital day, he suddenly failed, and died within thirty minutes.

#### DIFFERENTIAL DIAGNOSIS

DR. ALFRED O. LUDWIG: In this case, we are confronted with a man who was obviously suffering from hypertension, and we must decide what was the nature of the episodes of severe pain that finally led to his death. Not many conditions cause pain severe enough to be unrelieved by two injections of morphine. One immediately thinks either of extensive cardiac infarction or of some other serious vascular accident. I believe that the radiation of the pain, its character, his efforts "to walk it off" and the occurrence of cramps in the legs are all of great importance in the differential diagnosis.

In the first physical examination, the significant facts are the relatively slow and regular pulse, the apparent fall in blood pressure and the absence of a pericardial friction rub. These findings by no means finally exclude the presence of coronary occlusion. It would be somewhat unusual not to have more shock in the presence of coronary infarction of the severity indicated by the degree of pain that this man had. The absence of spasm in the epigastrium is evidence against such notable peritoneal irritation as would certainly follow any serious abdominal emergency like a ruptured viscus or acute inflammatory disease in this region. The slight elevation of the temperature is quite consistent with either coronary occlusion or any other severe vascular lesion.

The patient had moderate leukocytosis on this admission and a moderately elevated sedimentation rate, and these are of little help in differential diagnosis. The nonprotein nitrogen and renal-function tests indicate that no serious impairment of renal function had yet taken place as a sequel to the hypertension. The changes in the electrocardiogram are consistent with hypertensive heart disease with coronary involvement, but do not indicate the presence of acute occlusion. The x-ray films help us in ruling out a ruptured viscus in that they failed to show gas under the diaphragm, and also dispose of the gall bladder as the seat of this man's symptoms. One would like to know more about this area of decreased density overlying the fourth lumbar vertebra. Was there any evidence of erosion of these vertebrae? Could this mass represent dilatation or aneurysm of the abdominal aorta? The tortuosity of the aorta, as demonstrated by the chest films, is a further important point in the differential diagnosis, and further directs suspicion to this vessel. I do not believe that we can draw any valid conclusions from the intravenous pyelograms at this juncture. The gastrointestinal series serves to exclude the stomach as the seat of the lesion.



The most important statements in the next paragraph concern the course of the pain, which continued to be severe for six days, and the appearance of red blood cells in the urine, which suggests to me the possibility that some impairment of renal circulation may have developed. The second electrocardiogram does not convince me that coronary occlusion was present.

The pain returned soon after discharge, this time being more prominent in the chest. Physical examination on the second admission showed a rise in blood pressure over the previous reading. Most significant is the increase in dilatation of the aortic arch in the films taken at that time. The course in the hospital was notable for the occurrence of chest pain, with radiation down the arm, and diminution of the left radial pulse and of the blood pressure in this arm, suggesting impairment of the circulation to this arm, perhaps due to a lesion in the aortic arch.

On the third admission, there had been further extension of the process that had first appeared on the previous occasion and caused a fall in blood pressure in the left arm. The electrocardiogram suggested that there was definite involvement of the coronary tree, and the progressive changes in the T waves strengthen this belief. The fundal hemorrhages may have been secondary to the hypertension or due to interference with circulation. The symptoms on final admission spell further impairment of coronary circulation and rapid heart failure, with pulmonary and hepatic congestion, quickly followed by fatal circulatory collapse.

As I see this case, there is only one condition that satisfactorily explains all the signs and symptoms. I believe that this man had extensive arteriosclerosis of the entire aorta, and that he had successive episodes of dissection of the aortic wall secondary to small rents in the inner coat of this vessel. The first of these I believe took place in the lower thoracic or upper abdominal aorta. The dissection of blood down between the coats of the vessel temporarily interfered with circulation in the legs, as evidenced by the cramps on walking, and later with the renal blood supply, as shown by the appearance of hematuria. The second episode must have involved the aortic arch, with the dissecting blood constricting the mouths of the vessels arising from the arch that supplied the left upper extremity. The third episode may have represented further extension of the dissecting process in the arch to encroach on the coronary mouths and hence leading to coronary insufficiency. Finally, there was further extension in

the region of the arch, with further coronary constriction, cardiac collapse and death.

Most of the cases of dissecting aortic aneurysm that we have seen in this hospital have been acute and followed shortly by death. It is quite unusual for this condition to have so long a course as in this man, but such cases have been described. The severe character of the pain and its radiation to the back and shoulders, and later to the neck and arms, are quite characteristic of dissecting aortic aneurysm. When this condition involves the arch or thoracic portion of the vessel, it is commonly confused with coronary occlusion. In such cases, as in this, the absence of the characteristic electrocardiographic changes associated with acute coronary occlusion is a very helpful differential point. When the abdominal aorta is involved, an acute abdominal emergency may be simulated. I believe that the post-mortem examination will disclose the presence of cardiac hypertrophy secondary to the hypertension, extensive sclerosis of the entire aorta, with multiple dissecting aneurysms encroaching on the vessels of the arch, the coronary arteries and possibly the renal arteries. I do not believe that syphilis played any part in the production of the lesion in this case. It is very rare to obtain negative serologic findings in the presence of a syphilitic aortic aneurysm.

#### CLINICAL DIAGNOSES

Acute coronary occlusion.  
Hypertensive and coronary heart disease.

#### DR. LUDWIG'S DIAGNOSES

Essential hypertension.  
Hypertensive and coronary heart disease.  
Arteriosclerosis of aorta, with dissecting aneurysms of arch and thoracic and abdominal portions of aorta.

#### ANATOMICAL DIAGNOSES

Dissecting aneurysms of aorta, old, with rupture into right iliac artery, and fresh, with rupture into pericardium.  
Hemopericardium, with cardiac tamponade.  
Media necrosis aortica cystica.  
Compression of right renal artery, with atrophy of right kidney.  
Hypertrophy of left kidney.  
Nephritis, chronic vascular.  
Cardiac hypertrophy, hypertensive type.  
Arteriosclerosis, generalized: marked in aorta and coronary vessels.  
Bronchopneumonia, slight, of right lower lobe.

## PATHOLOGICAL DISCUSSION

DR TRACY B. MALLORY. Dr Ludwig has predicted with great accuracy our post mortem findings. At the time of the patient's first entry, there was lively discussion in regard to the diagnosis. Several persons, including Dr Wyman, Richardson and Dr. Edward F. Bland, stood out for dissecting aneurysm. A surgical consultant, however, was all for immediate transfer to the Surgical Service and exploratory laparotomy, although he never committed himself on paper to the precise type of surgical abdomen that he expected to find. Dr. Richardson, who was in charge of the service at the time, firmly refused to permit the transfer and remained unshaken in his diagnosis of dissecting aneurysm, even when the patient proceeded to make an unexpected complete recovery. On the second and third admissions, the symptoms were more limited to the cardiac area, and the events of the first admission were lost sight of, so that the final diagnosis on the death report was acute coronary occlusion, associated with hypertensive heart disease. On the final admission, however, Dr. Paul D. White again raised the question of dissecting aneurysm.

At the post-mortem examination, we found two separate dissecting aneurysms, clearly of different ages. The older one, which was obviously responsible for the events leading to the first admission, began with a horizontal tear on the anterosuperior aspect of the arch just distal to the subclavian artery at a point 9 cm. above the aortic valve. This led into smooth, endothelialized fat, which lay within the media of the vessel and nearly, but not quite completely, surrounded the

vessel. It had extended downward the entire length of the thoracic and abdominal aorta into the right common iliac artery, where it had reruptured through into the lumen of the latter vessel. This explains the temporary cramps in the right leg and their disappearance with the return of circulation. As evidence of the chronicity of this process, the lumen of the aneurysm was completely endothelialized and was, in fact, dotted with numerous small, bright-yellow plaques of atheroma. A second independent and evidently much more recent dissecting aneurysm began with another horizontal tear of the aortic intima 3 cm. distal to the first one but on the right posterior surface. In this case, the aneurysm had extended backward instead of forward down the ascending aorta to the annulus of the aortic valve, thus involving the mouths of both coronary arteries and that of the innominate artery. Three centimeters above the aortic valve, the outer layer had ruptured into the pericardium, which was distended with 500 cc of partly clotted blood. This aneurysm was obviously much fresher than the other, since it showed no endothelialization. We did not succeed in finding any trace of a third episode, such as Dr Ludwig suggested. Therefore, it is quite possible that the dissection of the second aneurysm occurred in more than one stage. It was of interest that the right kidney was only half the size of the left, and the right renal artery seemed considerably narrowed by the external pressure of the aneurysmal fat. The heart, as one would have expected, was considerably hypertrophied, and showed fairly marked atherosclerosis of most of the coronary branches, with numerous patches of narrowing but no foci of occlusion.

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established in 1828

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND  
PUBLISHED UNDER THE JURISDICTION OF THE COMMITTEE  
ON PUBLICATIONS

Official Organ of

THE MASSACHUSETTS MEDICAL SOCIETY  
and

THE NEW HAMPSHIRE MEDICAL SOCIETY

## EDITORIAL BOARD

Joseph Garland, M.D.	Stephen Rushmore, M.D.
William B. Breed, M.D.	Henry R. Viets, M.D.
George R. Minot, M.D.	Robert M. Green, M.D.
Frank H. Lahey, M.D.	Charles C. Lund, M.D.
Shields Warren, M.D.	John F. Fulton, M.D.
George L. Tobey, Jr., M.D.	A. Warren Stearns, M.D.
C. Guy Lane, M.D.	Dwight O'Hara, M.D.
William A. Rogers, M.D.	Chester S. Keefer, M.D.

## ASSOCIATE EDITORS

Thomas H. Lanman, M.D.	Donald Munro, M.D.
Henry Jackson, Jr., M.D.	
Walter P. Bowers, M.D., EDITOR EMERITUS	
Robert N. Nye, M.D., MANAGING EDITOR	
Clara D. Davies, ASSISTANT EDITOR	

SUBSCRIPTION TERMS: \$6.00 per year in advance, postage paid, for the United States (medical students, \$3.50 per year); Canada, \$7.04 per year, Boston funds; \$8.52 per year for all foreign countries belonging to the Postal Union.

MATERIAL for early publication should be received not later than noon on Friday.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston, Massachusetts.

## THE RESPONSIBILITIES OF HOSPITALS IN MATTERS OF CIVILIAN DEFENSE

A LARGE majority of the hospitals in Massachusetts have been asked to contribute directly, in one way or another, in the problem of civilian defense. Those that are to be used as emergency hospitals in the event of disaster must provide for adequate supplies and equipment and must so organize their professional and nonprofessional staffs on eight-hour or twelve-hour shifts that teams for the proper care of casualties will be available at a moment's notice. And those that are to serve as base hospitals must be prepared to receive and care for the large numbers of patients who will be evacuated, as soon as possible, from the emergency hospitals. Furthermore, Governor Saltonstall, in his proclamation dated January 8, ordered that "hospitals . . . shall be immediately

equipped for blackout." This does not mean that the order applies only to those hospitals that are to be used as emergency and base hospitals but rather to *all hospitals* within the Commonwealth, and the need for such a provision is obvious.

Although much has been asked of the hospitals in the emergency, it is no more than, or as much as, has been demanded of those who work in close association with them. Physicians have willingly responded to calls to military service, to the examining and advisory boards of the Selective Service System, to induction boards, to federal consulting boards and to the central, regional and local organizations of the Medical Division of the Massachusetts Committee on Public Safety. This exemplary response of the medical profession should serve as a pattern for hospital authorities. By promptly and efficiently meeting their responsibilities, they, too, can contribute wisely and effectively to the problems that confront the Commonwealth at this time.

## THE SCIENCE OF NUTRITION

THE world will always have to be patient with those who claim, and sympathetic with those who are required, to speak the truth, the whole truth and nothing but the truth, for as Anne Lindbergh observed, "To write or to speak is almost inevitably to lie a little." Our words fit our ideas so loosely. Even the mathematically efficient precision of modern gunnery must be concluded with the phraseology that the marksmanship was "poor" or "good," and in the case of the shell that struck the magazine of the battleship *Hood* the marksmanship was rightly termed "unfortunate." What would William of Orange say to the American columnists who keep repeating that England has not been invaded since the day of William the Conqueror? They have said it so often that many people now believe it to be a fact. Our minds move in tiny circles or leap great gaps of time or space with equal facility. Somehow, we rely on others to keep us from going too far astray.

On whom are we relying to keep our nutritional appraisals and advices within bounds? It is obvious that our nutritional status may not be at an

optimum because nobody knows what the optimum should be. It may even be admitted that there is a serious degree of malnutrition in this country, without throwing too much fat on the fire of the vitamin vendors. The stories of office girls who become listless when they are deprived of their thiamin, however, are reminiscent of the testimonials for Lydia Pinkham's vegetables, or whatever they were. Clinically visible nutritional deficiencies now attract our attention more readily, to be sure, but they are oftener secondary to alcoholism, dementia or advanced organic disease than to a lack of knowledge or economic resource. The gross nutritional lacks of twenty years ago have all but disappeared. What has become of the rickety baby? The adolescents of today are obviously larger and stronger than their parents are or ever were. For a nutritionist<sup>1</sup> to state that our food ways "are worse today than they were in 1914" seems ridiculous. Casual reading of some of his admonitions indicates that we have been going down the wrong road, or even moving backward, but when we see that they are based, among other things, on "many recent nutritional surveys including the extensive governmental study of consumer purchases conducted by the Bureau of Labor Statistics, the Bureau of Home Economics and the National Resources Committee," we begin to see the light.

The Science of Nutrition is being moved into the same apartment with Adequate Medical Care. It can pay the rent; it needs a better home and so is being moved. But it is a large family, which cannot possibly be completely housed even in spacious governmental bureaus; friends and relatives must be left behind who will continue to work under present conditions and with present scientific standards. There is going to be some temptation for those who have acquired new surroundings and new friends to forget their former associates, to forget the standards under which they previously lived and worked. There is going to be some pressure for them to keep up with the Joneses in the new neighborhood, where it is doubtless assumed that diets can be balanced with the same facility as budgets. The House of

Delegates of the American Medical Association has called at the new apartment and paid its respects in the form of a series of resolutions adopted at the Cleveland session, but the *Journal of the American Medical Association*<sup>2</sup> has also taken notice of the inspired character of some of the initial efforts. The medical profession may be counted on to back up any statement or program that is warranted by facts or good evidence, or even that is not too greatly exaggerated. Exaggerations, however, are seized on by publicists, who allow their stories to carry unintended implications, and this does the Science of Nutrition no good.

#### REFERENCES

1. Wilder, R. M. Nutrition in the United States. A program for the present emergency and the future. *Ann. Int. Med.* 14:2189-2198, 1941.
2. Editorial. National nutrition. *J. A. M. A.* 116:2854, 1941.

#### AN APPRECIATION

FRANK BURR MALLORY

1862-1941

It would appear to be a work of supererogation to discuss the record of Frank Mallory in the city and state that were his for fifty years, and yet he led an almost cloistered existence, which limited the opportunity to meet and know the man. Until the last year of his life, he was doing progressive work in an institute that properly bore his name, since he had demonstrated in his department that a lowly "city hospital" could be made to rival endowed research institutions. It is not my intent to write an obituary but rather an appreciation of a truly great man with whom it was my good fortune to be associated for many years.

One of Dr. Mallory's greatest contributions to the progress of medicine was undoubtedly his work on stains. He spent a year with Ziegler and Chiari in his early days in laboratory medicine, during the period when medical science was coming into flower in the Golden Age of German medicine. As one looks back to that period, it is remarkable to note the coming together of a literal constellation of geniuses, who suddenly appeared and co-operated in the launching of the new scientific medicine. Koch, Abbé, Weigert, Ehrlich and their colleagues, notably the group of fortunate bacteriologists who were in a position to take advantage of the opportunities presented by the new science, were destined to live in medical history.

Ziegler and Chiari were the pathologists of the group, giving special attention to the newer developments of pathologic histology. Weigert had focused attention on the aniline colors, which were an outgrowth from the English Perkins's ink, and microscopic pathology, crude up to then, became a highly specialized field that opened up new vistas in practical medical progress as well as in the field of pure science. Of Dr. Mallory's work in this



FRANK BURR MALLORY

field, Ewing has said, "The older pathologists had largely exhausted the possibilities of pathologic anatomy and histology, but it remained for Mallory, Ramon y Cajal and del Rio Hortega to carry histopathology to its highest development, and to make contributions beyond the reach of other methods."

These masters developed technics by which special tissues could be differentiated through tinctorial reactions. Dr. Mallory's interests began with efforts to more sharply label intercellular substances. Collagen, myoglia and neuroglia fibrils were in his special field of endeavor, and he first demonstrated and described fibroglia fibrils. His next interest was in the application of the new technic to the tracing of origins of cells from embryonal sources, in an effort to classify new growths more exactly. The results of his studies in these and other histologic fields were to revolu-

tionize laboratory practice in America. The laboratory horse-and-buggy period, referred to scornfully by the superior biologic chemist as the "hematoxylin-and-eosine period," was to come to an end. And yet it did not come to an end, or at least hematoxylin did not. Dr. Mallory was among the first to recognize the remarkable character of hematoxylin as a stain. His most selective staining method is that using phosphotungstic acid hematoxylin, and in his later years he was able to develop with hematoxylin a stain for traces of copper in tissues, more delicate than any chemical test. Morphology, banished as a dead subject, has come into its own again in its ability, with tinctorial aids, to do more exacting work than is possible by biochemical methods alone—to identify cells and observe by tinctorial procedures the chemistry of the individual cell.

Dr. Mallory's staining methods were to make his name familiar to laboratory men in all quarters of the globe. The brilliant results obtainable with his stains were arrived at only through exhaustive trial and error until the perfect method was achieved. He would work for months following leads that suggested the possibility of more specific differentiation of tissues or tissue products.

The sheer wizardry that can convert a commonplace coronary lesion, as seen in a section stained with hematoxylin and eosin, into a thing of beauty and distinction, as seen in a section stained by Mallory's aniline blue method, is alluring. It has a touch of Cinderella magic. The lipoid cells cease to be disembodied nuclei and become tangible objects with pink lacelike meshworks enclosing the spaces that had been occupied by the droplets of cholesterol esters. The collagen is a brilliant blue, the fibroglia fibrils are distinct, and the unstriped muscle of the media, bright red, becomes a tissue of quality instead of a bastard relative of the connective-tissue series. The fibrous tissue differentiates itself into young fibroblasts, older collagen-producing cells and frank hyaline scar tissue. With experience, one could almost write the natural history of the lesion without further information.

In this connection, a story told by Elliott Cutler is interesting. Dr. Cutler was working in Krehl's laboratory. The great man made his grand rounds of the laboratory at intervals. The worker stood rigidly at attention, facing his bench and the window, while the professor walked through behind him. If the master condescended to an interest in his work, the student was permitted to unbend and show his wares. Working next to Dr. Cutler was a graduate German student, Professor Marchand's son, who was doing an *Arbeit* on the brain. His sections were poor and badly stained

Dr. Cutler unearthed in the basement an abandoned paraffin microtome, which was finally coaxed into action. The resulting sections, which were fair, were stained by Mallory's phosphotungstic acid hematoxylin. When the great man made his next visit, he stopped at the student's bench, where he had never stopped before. There were explosive outbursts of "*Wunderbar! Wunder-schön!*" as the student explained the provenance of this remarkable exhibit. Dr. Cutler was called on, and told of his work with Dr. Mallory. "*Mallori, Mallori,*" exclaimed the professor, "I thought that he was an Italian."

Dr. Mallory's publications, apart from those on staining technic, were many and varied. His studies cleared the foggy atmosphere that surrounded the complicated pathology of typhoid fever. The paper on this subject, read before the Philadelphia Pathological Society, was illustrated by a series of eight magnificent color plates of drawings that might have served as a model for future medical illustration. However, the cost of such illustrations was almost prohibitive, and they were open to the criticism that, although they represented efforts at objective reproduction by the artist of actual microscopic fields, their delineation by human hands subjected them to possible bias, not with intent, but perhaps as the result of wishful thinking. For these reasons, Dr. Mallory turned to photographic reproductions and, in characteristic fashion, made himself a master of photomicrography. In his publication on the subject with Miss Leavitt, he disclosed the secrets of the art: "The first and greatest secret of good photomicrography is perfect sections, perfectly stained. . . . The second important point is choice of field." How often has he stressed the necessity of spending almost more time on the choice of fields for illustrations than on the writing of a paper! The lessons he taught in this respect resulted in a high quality of illustration in papers by his students, and elevated the level of scientific illustrations in American medical journals.

His studies of typhoid lesions brought out the activities of phagocytic cells, which arose from the endothelium of blood and lymph vessels and which he called endothelial leukocytes. The sources of these cells were widespread, as was their distribution, although the most important origin was the lymph and blood systems of the intestine, the seat of the primary focal infection. In this and further studies, it was recognized that the functions of the endothelial phagocytic cells were distinguished in general from those of the polymorphonuclear leukocytes. Although they did engulf certain bacteria (particularly tubercle bacilli), phagocytosis by the endothelial cells tended to be limited to other cells, particularly red blood cells and lymphocytes.

These studies included observations of mitoses in the endothelium of lymph and blood vessels and the migration of the endothelial leukocytes from the vessels into surrounding tissue. It was further recognized that many of the phagocytic cells passed through the liver and the lungs and thus into the systemic circulation.

Though Metchnikoff had developed his "theory of phagocytes" some years before this time, Mallory's studies of phagocytosis by cells of endothelial origin in human tissues were among the earliest published, were remarkable for their thoroughness of observation, preceded the studies of vital and supravital staining by colloidal dyes, and long antedated the Aschoff concept of the reticuloendothelial system.

The abundant pathologic material from the South Department of the Boston City Hospital was the basis for a series of studies of the pathology of the contagious diseases. A chapter on the pathology of diphtheria was contributed to the Cambridge University *Diphtheria*, edited by Nuttall and Graham-Smith, and papers were written on scarlet fever, measles and whooping cough.

The use of differential stains in determining the embryonal sources of tumor types was thoroughly investigated over a period of years, and the work formed the basis for the Middleton-Goldsmith Lecture of the New York Pathological Society for 1908. This and later papers on the microscopic anatomy and differentiation of cancer established Dr. Mallory's reputation as a national authority on tumors. With Dr. Gaylord, Dr. Weil and a few others, he formed the American Association for Cancer Research. The same group was responsible for stimulating the Congress of American Surgeons to develop interest in the education of the public with reference to cancer. Their action led ultimately to the formation of the American Society for the Control of Cancer.

In 1906, when the Harvard Medical School moved into the new and spacious buildings on Longwood Avenue, Dr. Mallory, under the heading "The Present Needs of the Harvard Medical School," appealed for endowment, not so much for the laboratory branches, although inadequate salaries were preventing men from entering these fields, but for clinical instructors "whose chief interests shall be teaching and scientific medical investigation."

At a time when the older conservative pathologists insisted that the Association of American Physicians was the national pathological society,

Dr. Mallory was one of the leaders in forming the American Association of Pathologists and Bacteriologists and was backed by the younger men in Boston. He took over the *Journal of Medical Research* on the death of Dr. Harold Ernst in 1923, and became its editor-in-chief. When the journal became the *American Journal of Pathology* and was made the official organ of the American Association of Pathologists and Bacteriologists, he remained as its editor-in-chief until 1940.

There arose a demand for a text on laboratory methods, which Dr. Mallory's training and experience and that of his colleague, Dr. Homer Wright, fitted them to satisfy. The familiar *Pathological Technique* was the answer, and has been the accepted authority on the subject since that time. The book represented the result of years of effort in the actual working out of laboratory procedure. With the pathologic material supplied by a large city hospital, supplemented by material from a large semipublic hospital, and added to by problem material referred to him from many sources, it was possible to determine the practical value of standard tests and to develop new procedures, which were improvements on the old or which entered new fields. Under the methods of laboratory study in the Boston City Hospital laboratory, which was early staffed with one or more residents and included a group of graduate students, exhaustive series of applications could be made of a test under investigation. In 1914 was published Dr. Mallory's *Principles of Pathologic Histology*, "which for reliability and detail has never been excelled in any language."

Dr. Mallory took great pride in the technic practiced in his laboratory. He used to refer with a chuckle to the custom of Chiari, who would rap the knuckles of his students if he caught them cutting thin sections. "*Nicht so dünn, nicht so dünn*" was his constant cry. Which reminds one of a famous American expert who is said to have announced, "Give me a good thick section of tissue fixed in formalin and stained with hematoxylin and eosin, and I am content," forgetting the amazing experience and expertness permitting him to make diagnoses under a technical handicap that would floor most if not all his colleagues.

Genius is the infinite capacity for taking pains. No person who was familiar with Dr. Mallory's studies on cirrhosis of the liver could question his tenacity, the exactness of his technic or the thoroughness with which he exhausted all the available experimental fields. His studies of the histology of cirrhosis disclosed the hyaline degeneration of liver cells, which is the distinguishing mark of alcoholic cirrhosis. Because his studies were

among the first by modern methods, it was his duty for thirty years to prove that ethyl alcohol was not the cause of the disease. As one genus of animals failed to respond, he turned to others, including many genera that had not before been used for laboratory purposes. He demonstrated, with Parker and Nye, that excess copper was the cause of pigment cirrhosis.

His manner of approach to a study of pathologic processes is illustrated in his introduction to a paper, "Cirrhosis of the Liver: Five different types of lesions from which it may arise." Cirrhosis, which becomes clinically manifest only in its later stages, had been studied almost wholly in its advanced, sclerotic form. Of this tendency, Dr. Mallory said: "In some organs the late stages of certain lesions have received more attention than the beginnings of these lesions. The emphasis has been placed on the wrong end of the process. . . . In order to understand a pathological process, it is necessary to find and study its beginning and to trace its biological development." This paper, beautifully illustrated, was read before the Johns Hopkins Medical Society. More recent studies have not improved on Dr. Mallory's classification of the cirrheses. He carefully refrained from limiting the causation of cirrhosis to the mechanisms responsible for the five types described. Recent demonstrations of the production of experimental cirrhosis by many agencies justify this caution.

Dr. Mallory lived an ascetic life. His training and experience taught him that the only way to do superlative work was to make that work an obsession, to avoid society and extracurricular demands. It is related that at a faculty function shortly after the birth of his older son, the irrepressible Dr. Arthur ("Patsy") Wentworth arranged with the faculty members that individually they should approach Dr. Mallory with a full glass of champagne and drink the health of the infant, with a hint at bottoms up. It is recorded that Dr. Mallory finished the ordeal with some of its original content of champagne still in his glass.

Austerity is almost a requisite in the public's mental picture of a scientist. To those who did not know Dr. Mallory, he appeared to be a perfect example of the genus, and yet he was intensely human. He had two sons and an army of adoptive sons, to use Sabatini's word, which I like, because it implies mutuality. He was as much interested in the young men who went through his laboratory as though they were his sons. The neophyte who was careless in thought or slovenly in action would feel the sharp edge of his tongue. But, once he had indicated his willingness, his intelligence and his capability, he had

in Dr. Mallory a friend who would help fight his battles. As Dr. Mallory said in his fifty-year class record (1886-1936), "Aside from the problems of my own line of work, one of my greatest pleasures has been in training young men and women in pathology and in seeing what they could make out of themselves under proper encouragement and stimulation; in other words, in getting them to do their own thinking and to work out their own salvation."

Dr. Mallory delivered a Harvey Lecture (1912) ("The Infectious Lesions of Blood Vessels"), the Mellon Lecture for 1925, the Hanna Lecture for 1925 ("Hemochromatosis and Chronic Poisoning with Copper") and the Shattuck Lecture for 1932 ("Cirrhosis of the Liver"). He was awarded the George M. Kober Medal for outstanding service in pathology by the Association of American Physicians. He was the third recipient of the gold-headed cane (following Dr. William H. Welch and Dr. Theobald Smith), given by Dr. Ernst to the American Association of Pathologists and Bacteriologists and awarded by them as a mark of distinguished service. He was a member of the Deutsche Pathologische Gesellschaft and of the Royal Medical Society of Budapest, an honorary member of the Pathological Society of Great Britain and Ireland and a fellow of the American Academy of Arts and Sciences. He was given honorary degrees of Doctor of Science by Tufts College and Boston University. In spite of his many honors, he never posed as a great man and was always available for counsel. The contrast between the autocratic practices in vogue in German laboratories and the procedure in Dr. Mallory's laboratory was great. He "sporting his oak" only when some trying bit of experimental work that would not brook interruption was under way. Remarkable to his friends was his ability to turn out progressive research under the constant interruptions that were a part of his daily life.

There was nothing of the "picturesque personality" in his make up. Diletantism, with all it implied, was abhorrent to him. He was inclined to be critical in his early days of those whom Weigert called Mr. Modifiers—Jones's modification of Brown's modification of Robinson's stain. He came, however, to appreciate that the modifiers were indicators of the progressive character of scientific medicine. They were emblems of dissatisfaction with things as they were at the moment, and marked a healthy state of discontent. He had great dislike for what he called "armchair pathologists," who capitalized the work of others, or depended on what Wright referred to with a sniff as "closet researchers."

Dr. Mallory not only placed his young men in positions for which they were fitted, but followed with fatherly interest their upward progress through the years. And the progress of the men who worked in his laboratory was quite constantly upward. Of professorial rank alone, forty men in American and Chinese schools were or are graduates of the laboratory, and nineteen of them were or are engaged in teaching pathology. Their training in the laboratory fitted them to direct similar work in any medical institution or to start with superior preparation in any of the clinical branches. When plans for a piece of research were in question or difficulties arose in the diagnosis of rare specimens, resort could be had to "The Chief" with assurance of his scientific interest and help. He retained up to the end an undiminished enthusiasm. When something new was brought to him or even something old in the preparation of which good work had been done, his eyes would light up with interest. His critical approval of a piece of original work—the metaphoric tap on the shoulder—was an accolade to be sought for and cherished.

This was a man!

T L

## MEDICAL EPONYM

### MOEBIUS'S SIGN

The first mention of this sign was made by Moebius in a review of Pierre Marie's *Contribution à l'étude et au diagnostic des formes frustes de la maladie de Basedow* (Paris, 1883). The review appeared in Schmidt's *Jahrbucher der inneren und auslandischen gesammten Medicin* (200: 98-100, 1883). A portion of the translation of the former follows:

Von Graefe has said that lessening or abolition of the synergetic movement of the upper lids in raising and lowering the eyes is pathognostic. The reviewer has failed to find Graefe's symptom in a series of cases including some with and some without exophthalmos. He not only disbelieves in its pathognostic character, but considers it rather rare. On the other hand, the reviewer has recently observed a disturbance of convergence in two patients with Basedow's disease, both of whom had a moderate bilateral exophthalmos of equal degree. If the patient was asked to fix his vision on the examiner's finger, both eyes looked to the right or to the left. That is, the patient fixed with one eye and the external muscles of the other eye contracted consensually. On monocular examination, both internal recti functioned normally. In a third patient with exophthalmos, the symptom was absent. Whether the phenomenon is directly dependent on the exophthalmos is uncertain.

The subject was again discussed, and observations in eight additional cases were reported, in an



article, "Über Insuffizienz der Convergenz bei Morbus Basedowii [Convergence Insufficiency in Basedow's Disease]," which was published in the *Zentralblatt für Nervenheilkunde, Psychiatrie und gerichtliche Psychopathologie* (9: 356-358, 1886).

R. W. B.

## MASSACHUSETTS MEDICAL SOCIETY

### COMMITTEE ON MATERNAL WELFARE

#### CAUSES OF MATERNAL DEATH IN MASSACHUSETTS DURING 1940 (*continued*)

##### ALBUMINURIA, TOXEMIA AND ECLAMPSIA

Twenty-four cases are classified under albuminuria, toxemia and eclampsia.

*Undelivered cases.* Six patients died undelivered.

Two weeks before term, one patient had a systolic blood pressure of 170, with a large amount of albumin. Hospitalization was advised and refused. The following day, the physician was notified that the patient was having difficulty in breathing. When he arrived, she was dead. Cerebral hemorrhage may have been the immediate cause of death.

Another patient had had no prenatal care, and convulsions were present when she reached the hospital. The systolic blood pressure was over 200. There was a large trace of albumin in the urine. No attempt was made to induce delivery, and the patient died shortly thereafter.

The next case occurred in a twenty-seven-year-old primipara who had had very poor prenatal care. When she arrived in the hospital, she had a blood pressure of 190 systolic, 110 diastolic. She had a large amount of edema. Convulsions appeared, and the patient was treated medically. No attempt at delivery was made.

The next patient, a multipara in her thirteenth pregnancy, had had no prenatal care. The blood pressure was 252 systolic, 152 diastolic. The patient died after receiving a few whiffs of chloroform for an emergency cesarean section.

Another patient died shortly after she reached the hospital. She was comatose when she arrived, and was treated with Veratrone and artificial respiration but never regained consciousness. This patient was very poorly treated during pregnancy. Autopsy showed that the immediate cause of death was hemorrhage about the medulla.

The last patient in this group was a primipara who had had inadequate prenatal care; when she arrived in the hospital, she was in convulsions and unconscious and died within a few hours.

In the cases referred to above, prenatal care was either absent or inadequate. To prevent such fatalities, patients must be taught to visit some physician regularly, and physicians must learn to see their patients regularly and attach more importance than these records show to increased blood pressure and albumin during pregnancy.

*Delivered cases.* Seventeen patients died after being delivered.

One of these had definite convulsions associated with a separated placenta; she was delivered by the Dublin method but died a few hours later.

Another patient went into labor spontaneously, and was delivered of a child by low forceps but died of eclampsia a few hours later. This patient had grossly inadequate prenatal care.

The next patient had been hospitalized for several weeks and died of a toxemia six hours after a normal delivery.

One patient developed eclampsia after a normal delivery and died two days later.

Another patient was seen frequently by her physician but was not sent into the hospital until convulsions appeared. The blood pressure was 220 systolic, 140 diastolic. She went into labor spontaneously and delivered a stillborn infant. She died five and a half hours after delivery. Although this patient had been frequently seen and apparently intelligently treated, the seriousness of the condition should have suggested the induction of labor much earlier. Had this been done, she probably would not have died.

The next patient, shortly after delivery, had what appeared to be convulsions and a cerebral hemorrhage, from which she did not recover.

One patient, who had been seen routinely during pregnancy and had been treated for syphilis, died eleven hours after delivery, apparently from circulatory collapse. She had had a systolic blood pressure between 150 and 160 and a good deal of albumin in the urine.

Another patient with increased blood pressure and albumin suffered separation of the placenta and died of anuria nine days after delivery.

The next patient was admitted to the hospital in labor. The blood pressure was 180 systolic, 100 diastolic. Following the first convulsion, she was delivered by version, even though the cervix was not fully dilated. The convulsions continued, and death occurred the same day.

One patient was said to have had a fulminating eclampsia. She delivered herself spontaneously and was doing well until three days following delivery, when she suddenly died, presumably of cerebral hemorrhage.

Another patient developed convulsions during

labor. The blood pressure was 176 systolic, 120 diastolic. Five more convulsions developed during the next twelve hours, and death occurred twenty-four and a half hours later.

The next patient, who had a blood pressure of 150 systolic, 130 diastolic, delivered herself of a macerated six months' fetus and presumably was doing well until a week later, when she developed a cerebral hemorrhage and died.

One patient was delivered by low forceps after a normal labor. She had previously shown increased blood pressure and albumin. She was brought into the hospital in coma, after having had a convulsion. There were five convulsions in all, and the patient died shortly after entry.

Another patient developed convulsions before delivery, and died shortly after the birth of twins.

The next patient, who had had excellent care during pregnancy, developed symptoms a week after the blood pressure and urine were normal. She had a separation of the placenta and died of a cerebral hemorrhage.

One patient, who had not been seen at all during pregnancy, had convulsions and did well so far as the toxemia itself was concerned, but died eighteen days later of a complicating pneumonia.

Two cases of toxemia were associated with cesarean section. One patient appeared in the hospital with convulsions. An emergency cesarean section was done, and she died of anuria three days later. An attempt to induce labor by rupturing the membranes was reported in the second case. This was not satisfactory, and since the patient was rapidly failing and labor had not started, a classic cesarean section was done, and she died the following day.

The most striking thing about this series is the number of patients who died of cerebral hemorrhage. There are three cases in which operative treatment can be criticized. The first is that of the patient who was delivered by version before full dilatation. It is believed that if labor does occur, the patient should be left alone until full dilatation, and that she should be allowed to deliver herself if the second stage is not prolonged. The other two are those in which cesarean section was performed. In cases of definite eclampsia, it is agreed that conservative treatment gives far better results.

#### TRANSFUSION

In 1940, 8 deaths were directly attributed to transfusion. One patient had been delivered by low forceps after a moderately rapid labor, and suffered a moderate post-partum hemorrhage. Transfusion was followed by a reaction within twenty minutes, which was evidenced by a severe

chill, an elevation of the pulse rate and lowered blood pressure. The donor and recipient were both in Group IV.

The next case in which incompatible transfusion was the result of death occurred in a woman who had had a severe post-partum hemorrhage associated with an inverted uterus. She had eight blood transfusions, and ultimately died of anuria.

One case occurred in a multipara who had a normal labor when about seven months pregnant and spontaneous delivery of a macerated fetus. She was brought to the hospital a few days later because of secondary anemia and a moderate degree of puerperal sepsis. A transfusion of citrated blood was immediately given, the bloods being typed and cross matched. Anuria and generalized edema set in, and death occurred twelve days later.

Another case was associated with an operation for rupture in a tubal pregnancy. Transfusion was done following the operation, and suppression of urine immediately set in. The patient died of uremia fifteen days after operation.

The next patient was a primipara, who suffered moderate post-partum hemorrhage following a forceps delivery. On the following day, the hemoglobin was 45 per cent and the red cell count 2,410,000. Fifteen minutes after a transfusion of citrated blood was started, the patient became weak and complained of loss of vision. Death occurred an hour and a half later.

One case occurred in a patient suffering from mitral stenosis with decompensation. When she was about four months pregnant, therapeutic abortion was performed. Because of hemorrhage, citrated blood from a donor of the same blood group as the patient was started shortly after the operation, but because of cyanosis and a severe chill was stopped after a small amount had been introduced. On the following day, another transfusion with the same blood was completed; death occurred eight hours later.

The next patient who died as a result of transfusion was a primipara who had had a difficult operative delivery. Three hundred and fifty cubic centimeters of blood from a donor of the same group, after direct matching, was administered. The patient became anuric and died forty-eight hours later.

The last case was associated with a transfusion following a cesarean section. Shortly after the transfusion was started, the patient had a severe reaction, and a complete suppression of urine followed. Death occurred two days later.

Although some of these deaths may have involved the Rh factor,—a circumstance whose sig-

nificance is becoming more generally recognized and appreciated,—the fatal outcomes in the majority of cases are inexcusable and clearly point out the need for more carefully and accurately performed compatibility tests.

#### PERNICIOUS VOMITING

Two patients died as a result of vomiting of pregnancy. One was approximately four months pregnant when pregnancy was interrupted by the introduction of a catheter, in addition to cervical packing. This patient entered the hospital with a temperature of 101°F., and died four days after admission to the hospital.

The other patient, who was sent into the hospital when about three months pregnant, had been vomiting continuously for eight weeks. She was aborted, but death followed.

Both these patients were treated conservatively too long before interference. Modern treatment—consisting of early hospitalization, intravenous therapy and intramuscular thiamin chloride—is so successful that therapeutic abortion is seldom necessary.

#### MESENTERIC THROMBOSIS

Mesenteric thrombosis was the cause of death in 2 cases. In one of these, the initial abdominal pain came on three hours after normal delivery. Laparotomy was performed thirteen hours later, when the diagnosis of mesenteric thrombosis was confirmed. The patient died forty hours after operation.

The other case of mesenteric thrombosis followed cesarean section. The acute symptoms appeared four days after the patient had been operated on. The patient died twenty-four hours later. The diagnosis was confirmed by autopsy.

These cases are extremely interesting and, fortunately, very unusual.

#### SEPSIS

A more careful review of the deaths in 1940 resulted in the classification of another case in which death was associated with sepsis. This patient had a diaphragmatic hernia; when she was about three months pregnant, it was decided, after medical and surgical consultations, that the hernia would make it unsafe for pregnancy to continue; hence, abortion was advised. No obstetrician saw this patient. An autopsy showed that the patient died of sepsis. The bacteriologic diagnosis was "gas bacillus, hemolytic type."

#### SURGICAL SHOCK

In 1 case, which is still under investigation by a medical examiner, death apparently resulted

from surgical shock following a ruptured bladder. The patient was found dead in an apartment house.

#### TREASURER'S NOTICE

The *New England Journal of Medicine* is sent to all fellows whose dues are fully paid. After March 1, names of delinquent fellows are dropped from the mailing list. All fellows are urged therefore to send, before March 1, their dues for the current year to their district treasurers.

CHARLES S. BUTLER, M.D., *Treasurer*

#### DEATHS

BRAGG—FRANCIS A. BRAGG, M.D., of Foxboro, died February 6. He was in his seventy-eighth year.

Born in Shutesbury, Dr. Bragg received his degree from Harvard Medical School in 1894. He was medical examiner for the Sixth Norfolk District and was a member of the Massachusetts Medical Society and the American Medical Association.

He is survived by his widow, a daughter and two sons.

LOURIE—OSIP R. LOURIE, M.D., of Boston, died recently. He was in his sixty-ninth year.

Born in Russia, Dr. Lourie received his degree from the University of St. Vladimira Faculty of Medicine, Kiev, in 1896. He came to the United States in 1922, and practiced in Boston until his death. He was a fellow of the Massachusetts Medical Society and the American Medical Association.

His widow survives him.

TEN BROECK—STANTON J. TEN BROECK, M.D., of Orange, died January 14. He was in his seventy-first year.

Born in Hillsdale, New York, Dr. Ten Broeck received his degree from New York University Medical College in 1893. He was a member of the Massachusetts Medical Society and the American Medical Association.

He is survived by his widow, a son, three grandchildren and a sister.

#### WAR ACTIVITIES

##### UNITED STATES NAVY

The following medical officers of the United States Naval Reserves of the First Naval District have been assigned to active duty outside the First Naval District:

Allen, E. C., Lieut. (JG)

Bean, H. C., Comdr.

Belcher, C. D., Lieut. (JG)

Benson, H. L., Lieut. (JG)

Bigelow, R. B., Lieut. Comdr.

Bird, L. C., Lieut.

Boguniechi, S. J., Lieut. (JG)

Bronstein, B. R., Lieut. (JG)

Carlton, W. T., Lieut. (JG)

Carmody, R. F., Lieut. (JG)

Chamberlain, J. W., Lieut.

Cheever, F. S., Lieut. (JG)

Chesbro, W. L., Lieut.

Cone, T E, Jr, Lieut (JG)  
 Cruickshank, F S, Lieut. Comdr  
 Cummings, G E, Lieut (JG)  
 Farnsworth, D L, Lieut  
 Farrington, R F, Lieut. (JG)  
 Feldman, N N, Lieut (JG)  
 Fitzpatrick, W J, Jr, Lieut (JG)  
 Fleischer, H W, Lieut (JG)  
 Forbes, W W, Lieut (JG)  
 Fothergill, L D, Lieut Comdr  
 Fregosi, H J, Lieut.

Garrey, W E, Lieut  
 Gauld, A G, Lieut  
 Giuffrida, F, Lieut (JG)  
 Glazer, L, Lieut.  
 Gleason, R S, Lieut  
 Glickman, A M, Lieut  
 Goldblatt, H W, Lieut (JG)

Haddad, A K, Lieut (JG)  
 Halbach, R M, Lieut Comdr  
 Haslam, E T, Lieut (JG)  
 Hayes, J J, Lieut (JG)  
 Helgeson, U H, Lieut Comdr  
 Herrick, C A, Lieut (JG)  
 Higgins, R F, Lieut (JG)  
 Hinman, H E, Lieut (JG)  
 Hoey, W O, Lieut  
 Hopkins, H P, Lieut (JG)

Kepnes, H A, Lieut (JG)  
 Kovarkian, A V, Lieut

Leighton, H T, Lieut (JG)  
 Levin, O, Lieut (JG)  
 Lowd, H M, Jr, Lieut (JG)  
 Lozner, E L, Lieut (JG)  
 Lulow, W V, Lieut (JG)

Marks, H B, Lieut (JG)  
 McLean, E B, Lieut.  
 McWilliams, J G, Lieut (JG)  
 Merrill, W, Lieut  
 Miller, D G, Lieut. (JG)  
 Miller, J Y, Lieut (JG)

Nichols, I C, Lieut Comdr  
 Nunes, J E, Lieut

Osterheld, R G, Lieut.  
 O Toole, J B, Lieut. (JG)

Page, R S, Jr, Lieut (JG)  
 Peters, J M, Lieut (JG)  
 Pippitt, R B, Lieut (JG)

Robinson, N D, Lieut  
 Ross, S, Lieut Comdr  
 Rothblatt, B W, Lieut (JG),

Schurmer, A F, Lieut  
 Schmidhofer, E, Jr, Lieut (JG)  
 Schwab, W J, Lieut. (JG)  
 Segal, S A, Lieut. Comdr  
 Shaw, C C, Lieut. Comdr  
 Shaw, E A, Lieut (JG)  
 Smith, E L, Lieut. (JG)  
 Smith, K E, Lieut. (JG)  
 Sommer, F X, Lieut (JG)  
 Stanbury, J B, Lieut (JG)  
 Stephens, H F, Lieut. (JG)

Tenney, B J, Lieut Comdr  
 Truslow, J B, Lieut. (JG)  
 Young, V T, Lieut (JG)  
 Zupanic, R, Lieut (JG)

## MISCELLANY

### NOTES

Sixteen appointments to the teaching and research staffs of the Harvard Medical School, the Dental School and the new School of Dental Medicine, effective during the present academic year, were recently announced as follows

*Medical School* Edward B D Neuhauser, of Cambridge, M.D., University of Pennsylvania '34, instructor in roentgenology, Vincent J Kelley, of Newton, M.D., Tufts, '25, assistant in laryngology, Sydney Ellis, of Boston Ph.D., Boston University '41, research fellow in pharmacology, James T Heyl, of Philadelphia, M.D., Harvard '37, research fellow in medicine John A Degen, Jr, of Chestnut Hill, M.P.H., Johns Hopkins '41, assistant in preventive medicine and epidemiology, Frederic W Rhineland, II, of Meadowbrook, Pennsylvania, M.D., Harvard '34, assistant in orthopedic surgery, Sam T Gibson, of Atlanta, Georgia, M.D., Emory University '40, research fellow in medicine, Earl H Wood, of Philadelphia, Ph.D., University of Minnesota '40, instructor in pharmacology, Gordon J Axelson, of Chicago, M.D., Duke University '37, assistant in medicine, Donald P Ham, of Mattapan, M.D., Boston University '38, assistant in roentgenology, Magnus I Smedal, of Waban, M.D., Harvard '29, assistant in roentgenology, William H Watters, of Boston M.D., Boston University '01, instructor in legal medicine, and Victor G Balboni, of Boston, M.D., Harvard '39, research fellow in medicine

*Dental School* Leonard N Donsanto, of Brighton, D.M.D., Harvard '38, assistant in oral surgery, and Wallace J Gardner, of Cambridge, D.M.D., Harvard '39, assistant in roentgenology

*School of Dental Medicine* John W Cooke, of Boston, D.M.D., Harvard '18, lecturer on clinical dentistry

The Trustees of Middlesex University announce that at a meeting held on February 9 they appointed Dr Stephen Rushmore as dean of the School of Medicine to take office on February 11, 1942

### ANNUAL MORTALITY SUMMARY FOR 1941

The number of deaths in eighty-eight major cities in the United States during 1941 decreased 0.4 per cent as compared with the 1940 figure for the same group of cities on the basis of provisional reports. There were 443,782 deaths reported in 1941 as compared with 445,504 deaths for the corresponding group of cities in 1940.

Except for three periods during the year, the weekly death rates for the major cities in the United States in 1941 were generally below those for the average death rates for the three year period, 1938-1940, inclusive. The first peak in the weekly mortality rates, which occurred in January and February, corresponded with the period of the influenza epidemic (see cut). Two conspicuous in

creases in mortality rates, in the latter part of June and in early August, were closely related to the heat waves that occurred over a large portion of the country.

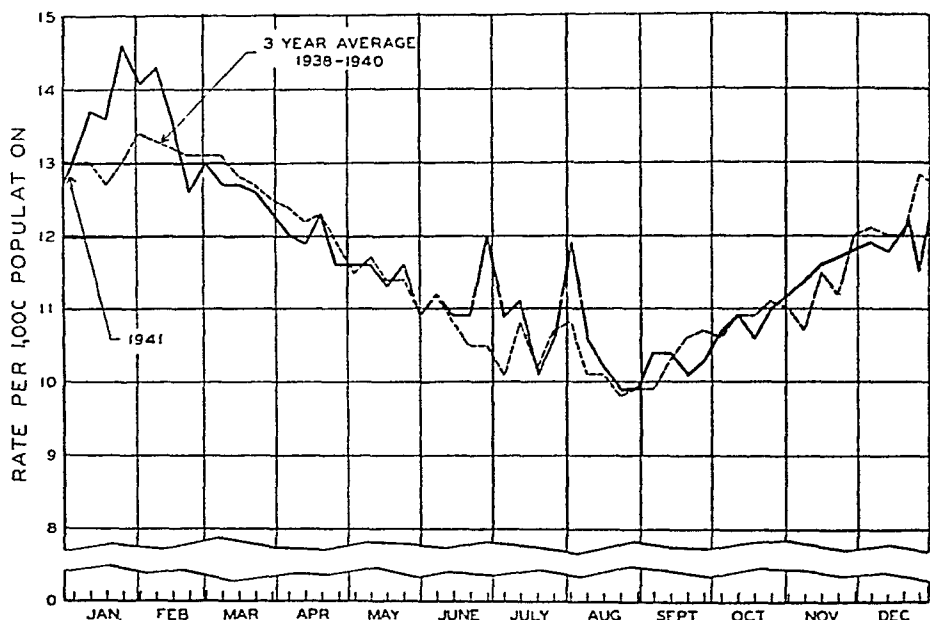
The 28,166 infant deaths reported for 1941 represent an increase of 1319, or 4.9 per cent, over the 26,847 infant

represents a decrease of 8.9 per cent as compared with the final mortality rate of 40.5 for 1940.

In the comparison of death rates, it should be noted that the rates are based on the population as enumerated in the 1940 census. Inasmuch as there has been an unusual

### DEATH RATE BY WEEKS IN MAJOR CITIES

[RATE BASED ON 1940 ENUMERATED POPULATION]



deaths reported for 1940. However, on the basis of the provisional figures, the infant death rate for 1941 was 36.9 infant deaths per 1000 estimated live births, which

amount of population movement since the population census was taken, the rates for individual cities need to be interpreted with a certain degree of caution.

### BOOK REVIEWS

*Clinical Immunology, Biotherapy and Chemotherapy in the Diagnosis, Prevention and Treatment of Disease.* By John A. Kolmer, M.D., and Louis Tuft, M.D. 8°, cloth, 941 pp., with 27 illustrations, including 11 color plates. Philadelphia: W. B. Saunders Company, 1941. \$10.00.

This large and comprehensive volume suffers from the defects common to all textbooks that attempt to cover a vast and rapidly changing field. It is written by two distinguished authorities for the benefit of students and practitioners, and contains a mass of useful, practical information on the technic of performing tests within the scope of ordinary medical practice. There is probably no other book in which such a variety of practical data on the diagnosis, treatment and prevention of every sort of infectious disease is assembled. Because of its all-inclusiveness, the book is spotty. Too much space is devoted to many time-honored methods of treatment that are of dubious value, such as nonspecific protein and vaccine therapy. There are some glaring omissions, such as failure to discuss fever therapy in the section on gonococcal infections. But all in all, this volume represents a conscientious attempt to present to the practicing physician the theoretical and technical knowledge that is essential to the understanding and treatment of infectious disease. Such a book serves a useful function when the biologic and chemotherapeutic armamentarium is so extensive. The work is very much up to date, but in places a more critical appraisal of very recent methods of treatment would be better.

Although this book will not replace a consultant when the life of a patient is at stake, practitioners will find it

an extremely useful guide in the handling of patients with all sorts of infectious and allergic conditions.

*Medical Diagnosis and Symptomatology.* By Samuel A. Loewenberg, M.D. Fifth edition, entirely revised and reset. 4°, cloth, 1139 pp., with 520 illustrations. Philadelphia: F. A. Davis Company, 1941. \$12.00.

In the review of the first edition of this book (*New Eng. J. Med.* 201:199, 1929), attention was called to the fact that the book represented an expansive effort to encompass the field of physical diagnosis and clinical and laboratory medicine within the confines of an ordinary textbook. Although the format and arrangement have been modified, the scope of the book is unchanged. In the opinion of the reviewer, the net result can be summarized as a fair textbook of physical diagnosis that is grossly inadequate in all other respects. The symptoms of lobar pneumonia are described in about eighty words, and those of pulmonary tuberculosis in thirty-six words; and throughout the book, such superficial and sketchy descriptions abound.

Despite the fact that it has now reached the fifth edition, many errors of omission and commission are still noted. Thus, hyperthyroidism is not included in the differential diagnosis of mitral stenosis, and the sharpness of the first heart sound in hyperthyroidism is not mentioned. In describing the duration of the organic murmur, the author states that it "occupies nearly the whole of the systole, diastole or presystole." Under exophthalmos, the pulsating type is omitted. Space does not permit mention of a number of others. What might have been a good textbook of physical diagnosis appears, to the reviewer, to be less than a mediocre book on medicine.

## NOTICES

## ANNOUNCEMENT

DR HUGO B C RIEMER announces the removal of his Boston office from 128 Newbury Street to 29 Commonwealth Avenue

BOSTON DOCTORS  
SYMPHONY ORCHESTRA

The Boston Doctors' Symphony Orchestra will rehearse, under Alexander Thiede, every Thursday at 8 30 p.m. at Station WMEX, 70 Brookline Avenue, Boston. Those interested in becoming members should communicate with Dr Julius Loman, 520 Beacon Street, Boston (KEN 3200 or LON 2155)

Communicate with Dr Julius Loman, 520 Beacon Street, Boston (KEN 3200 or LON 2155)

## HARVARD MEDICAL SOCIETY

A meeting of the Harvard Medical Society will be held in the amphitheater of the Peter Bent Brigham Hospital on Tuesday, February 17, at 8 15 p.m.

## PROGRAM

## Clinical presentation

The Pathology of Peripheral Neuritis Dr Derek Denny Brown

Physicians and medical students are cordially invited to attend

## BOSTON LYING IN HOSPITAL

A meeting of the Journal Club of the Boston Lying in Hospital will be held at the hospital on Wednesday, February 18, at 8 15 p.m. Dr Frank Barton, of the Massachusetts Memorial Hospitals, will speak on 'The Blood Bank and the Emergency'

Physicians and medical students are cordially invited to attend

## BOSTON SOCIETY OF BIOLOGISTS

A meeting of the Boston Society of Biologists will be held in the Eastman Lecture Room (G-120), Massachusetts Institute of Technology, on Wednesday, February 25, at 8 p.m.

## PROGRAM

Serum and Tissue Phosphatase in Experimental Scurvy Drs B S Gould and H Schwachman

The Biological Action of Short Waves A method for the determination of the local distribution and dosage Dr K. S. Lion

X-ray Diffraction and Electron Microscope Studies of Collagen Fibers Dr R S Bear, Mr C E Hall, Miss M A Jakus and Professor F O Schmitt

After the meeting, there will be a demonstration of the electron microscope and other biophysical apparatus in the Biological Laboratories

## BOSTON MEDICAL HISTORY CLUB

The Boston Medical History Club will hold its fourth meeting of the season at the Boston Medical Library on Wednesday, February 18, at 8 15 p.m. Dr John Romano

will speak on 'Early Contributions to the Study of Delirium Tremens'

All interested persons are cordially invited to attend

## MASSACHUSETTS MEMORIAL HOSPITALS

A staff meeting of the Massachusetts Memorial Hospitals will be held in the Evans Memorial Auditorium on Friday, February 27, at 8 15 p.m.

## PROGRAM

Report on the Laboratory Department Dr Charles F Branch

Carcinogenesis as a Conditioned Deficiency Dr Cornelius P Rhoads, director of the Memorial Hospital for Cancer and Allied Diseases, New York City

## JEWISH MEMORIAL HOSPITAL

A diagnostic and therapeutic conference will be held at the Jewish Memorial Hospital on Thursday, February 19, at 11 a.m. Dr Joseph C Aub will speak on 'Endocrine Problems'

Physicians and medical students are cordially invited to attend

## WALTHAM MEDICAL MEETING

The regular clinicopathological staff conference of the Metropolitan State Hospital will be held at the hospital on Wednesday, February 18, at 8 p.m. Drs Clementine McKeon and Richard C Wadsworth will present, 'Two Cases of Carcinoma, with Metastases to the Vertebra, Causing Great Pressure and Neurological Complications'. Dr Walter Wegner will lead the discussion.

All interested physicians are cordially invited to attend

## NEW ENGLAND PATHOLOGICAL SOCIETY

There will be a meeting of the New England Pathological Society at the Pathology Amphitheater of the Massachusetts General Hospital on Thursday, February 19, at 8 00 p.m. The exhibit room will be open at 7 30 p.m.

## PROGRAM

Exhibit of Pulmonary Surgical Specimens Drs R Klopstock, E D Churchill and Benjamin Casleman

Subdural Abscess A clinicopathologic study Drs C S Kubik and R D Adams

Isolation of Pleuropneumonia Like Organisms from Human Patients Drs W E Smith and L Dienes

The Nature of Pleuropneumonia Like Organisms Dr L Dienes

Renal Biopsies from Hypertensive Patients Dr Benjamin Castleman

Business meeting

Collation

## NEW ENGLAND HEART ASSOCIATION

A meeting of the New England Heart Association will be held in the Evans Memorial on Wednesday, February 25, at 8 15 p.m. It should be noted that the date has been changed from that originally announced

## PROGRAM

Effect of Venous Obstruction on Blood Flow in the Limbs Drs C K Friedland and R W Wilkins

Congenital Mitral Stenosis and Atresia Dr A S Nadus

Blood and Cell-Volume Determinations with Radioactively Tagged Erythrocytes. Drs. J. F. Ross and M. A. Chapin.

Ultimate Effect of Pregnancy on Rheumatic Heart Disease. Dr. N. H. Boyer.

Some Remarks Concerning the Clinical Diagnosis of Pulmonary Embolism and Infarction. Dr. Chester S. Keefer.

Interested physicians and medical students are cordially invited to attend.

#### NEW ENGLAND SOCIETY OF PHYSICAL MEDICINE

A regular meeting of the New England Society of Physical Medicine will be held at the Hotel Kenmore, Boston, on Wednesday, February 18, at 8 p.m. Dr. John H. Talbott will speak on "Physiologic and Therapeutic Effects of Hypothermia." Dr. Augustus Rose will lead the discussion. A council meeting will be held at 6 p.m., followed by an informal dinner in the Empire Room at 6:30.

All interested physicians are cordially invited to attend the meeting.

#### HEMATOLOGY JOURNAL CLUB

There will be a meeting of the Hematology Journal Club at the Joseph H. Pratt Diagnostic Hospital, Thursday, February 26, at 8:15 p.m.

##### PROGRAM

Discussion of cases.

Discussion of sickle-cell anemia.

Physicians and medical students are cordially invited to attend.

#### AMERICAN CONGRESS ON OBSTETRICS AND GYNECOLOGY

The second American Congress on Obstetrics and Gynecology will be held in St. Louis, Missouri, April 6 to 10, 1942. All the meetings and the commercial, educational and scientific exhibits will be held in the Public Auditorium.

The general plan for the program will be much the same as that of the first congress, which was held in Cleveland in 1939, with sectional meetings for the various groups (nurses, public-health officers, administrators, educators and physicians), general sessions for all members attending the congress and round-table discussions. The evening sessions will be open to the general public.

Admission to the congress will be by membership cards only, which may now be secured by the payment of a \$5.00 registration fee. All mail should be addressed to and further information may be obtained from the American Congress on Obstetrics and Gynecology, 650 Rush Street, Chicago.

#### UNITED STATES CIVIL SERVICE EXAMINATION

##### Orthopedic Mechanics

An examination has been announced by the Civil Service Commission to secure orthopedic mechanics for the Army services. The salary is \$2000 a year. Persons may qualify under the following optional subjects: General, bracemaker, shoemaker and leatherworker, and limb-maker. Because of the demand for qualified eligibles,

applications will be accepted at the Commission's Washington office until further public notice.

Persons appointed will construct, design, alter and repair orthopedic appliances as indicated by the optional subjects. This includes working from living models and plaster casts, doing nickel plating, and shaping, grinding, and polishing metals used in orthopedic appliances.

Applicants will not take a written test, but will be rated on the extent and quality of their experience. They must have had five years of appropriate experience in orthopedic work within the past ten years. Under the option "shoemaker and leatherworker," persons whose experience has been in general shoe repair will not be considered qualified.

Examination announcements and application forms may be obtained at first-class and second-class post offices and from the Civil Service Commission, Washington, D. C.

#### SOCIETY MEETINGS AND CONFERENCES

##### CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING SUNDAY, FEBRUARY 15

###### MONDAY, FEBRUARY 16

12 15-1 15 p.m. Clinicopathological conference. Peter Bent Brigham Hospital amphitheater.

###### TUESDAY, FEBRUARY 17

\*9 00-10 00 a.m. Medical clinic. Dr. S. J. Thannhauser Joseph H. Pratt Diagnostic Hospital

\*12 00 m. Chemotherapy. Dr. Maxwell Finland South End Medical Club Headquarters of the Boston Tuberculosis Association 571 Columbus Avenue, Boston.

12 15-1 15 p.m. Clinicoroentgenologic conference. Peter Bent Brigham Hospital amphitheater.

8 15 p.m. Pathology of Peripheral Neuritis Dr. Derek Denys Brimley Harvard Medical Society, Peter Bent Brigham Hospital amphitheater.

###### WEDNESDAY, FEBRUARY 18

\*9 00-10 00 a.m. Recent Advances in Allergy Dr. E. A. Cowdrey Joseph H. Pratt Diagnostic Hospital.

\*12 00 m. Clinicopathological conference. Children's Hospital

12 00 m. The X ray in Diseases of the Digestive Tract and Biliary System. Dr. Samuel A. Robins and his associates Boston Gastroenterological Society, Beth Israel Hospital.

\*8 00 p.m. Physiologic and Therapeutic Effects of Hypothermia Dr. John H. Talbott. New England Society of Physical Medicine Hotel Kenmore, Boston.

\*8 15 p.m. Early Contributions to the Study of Delirium Tremens Dr. John Romano. Boston Medical History Club, Boston Medical Library.

\*8 15 p.m. The Blood Bank and the Emergency Dr. Frank E. Boston Lying-in Hospital.

\*8 30 p.m. The Use of Drugs in the Treatment of Alcoholism Dr. Wilfred Bloomberg. Washingtonian Hospital.

###### THURSDAY, FEBRUARY 19

\*9 00-10 00 a.m. Medical clinic. Dr. S. J. Thannhauser Joseph H. Pratt Diagnostic Hospital.

\*11 00 a.m. Endocrine Problems Dr. Joseph C. Aub Jewish Memorial Hospital.

8 00 p.m. New England Pathological Society. Massachusetts General Hospital.

###### FRIDAY, FEBRUARY 20

\*9 00-10 00 a.m. Clinical and Experimental Observations on the Use of Thyrothricin in the Treatment of Infections Dr. C. H. Kamp. Joseph H. Pratt Diagnostic Hospital.

###### SATURDAY, FEBRUARY 21

\*9 00-10 00 a.m. Sulfur Metabolism Dr. Martin Nothmann Joseph H. Pratt Diagnostic Hospital

\*Open to the medical profession.

FEBRUARY 18 Waltham Medical Meeting Page 289.

FEBRUARY 19-21. American Orthopsychiatric Association Page 768 Issue of October 30

FEBRUARY 20-21 New York University College of Medicine Page 2 Issue of January 29.

FEBRUARY 25. Boston Society of Biologists Page 289.

# The New England Journal of Medicine

Copyright 1942 by the Massachusetts Medical Society

VOLUME 226

FEBRUARY 19, 1942

NUMBER 8

## RECURRENT PYELONEPHRITIS DURING PREGNANCY\*

GEORGE C. PRATHER, M.D.,† AND WESTON SEWALL, M.D.‡

BOSTON

**A**FTER completion of a pregnancy during which pyelonephritis has been a complication, both the patient and her physician are interested in the question, Will there be a recurrence of recurrence, as well as the factors that may influence a recurrence, are the purpose of this paper, the data were derived from the records of 72 patients with pyelonephritis asso-

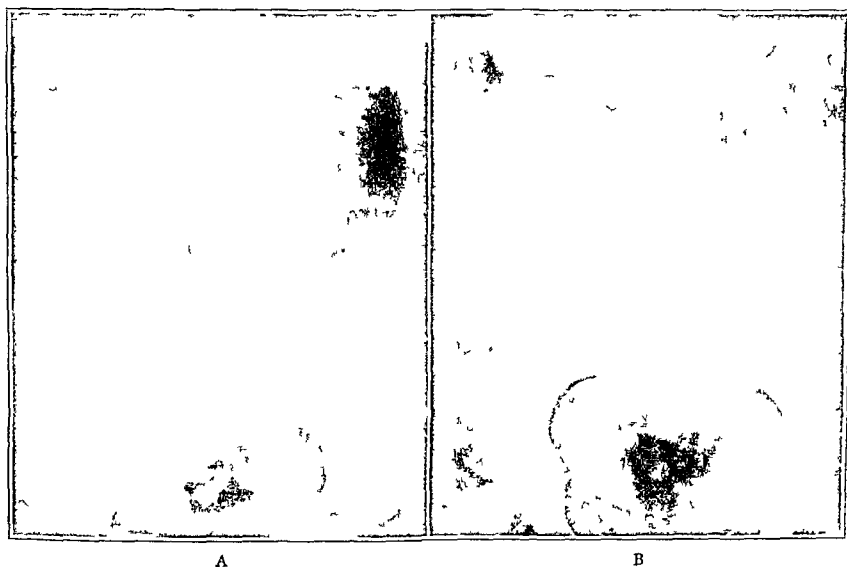


FIGURE 1

*This patient, a para II had a right pyelonephritis during the seventh month of pregnancy. A shows the pyelographic changes in the pelvis and ureter. B, taken three years later when the patient was again pregnant, shows nearly identical anatomic changes.*

rence of "pyelitis" if another pregnancy ensues? An answer, not necessarily correct for an individual, can be given on a statistical basis. The

\*From the Urological Department and Obstetrical Department, Boston Lying-in Hospital.

†This factor in general surgery, Harvard Medical School, assistant urologist, Boston Lying-in Hospital.

‡Assistant in obstetrics, Harvard Medical School, assistant obstetrician to outpatients, Boston Lying-in Hospital.

ciated with pregnancy who later returned to the hospital for one or more subsequent pregnancies.

During their first pyelonephritis of pregnancy, 70 of the 72 patients had pyelonephritis before delivery, in 2, the pyelonephritis occurred immediately afterward. Forty-three patients were in a febrile phase while in the hospital, and 29 were



admitted or seen following their febrile attack. Approximately 58 per cent were primiparas. A past history indicative of an inflammatory type of kidney disease was obtained in 17 per cent. Urinary studies demonstrated a bacillary type of infection in 91 per cent, gram-positive cocci in 5 per cent and mixed infection in 4 per cent. The clinical findings indicated involvement of the right kidney alone in 48 per cent, bilateral disease in 32 per cent and left renal infection alone in 20 per

cent developed pyelonephritis in subsequent pregnancies; the remainder — about 12 per cent — had toxemia in subsequent pregnancies. The 17 patients who developed recurrent pyelonephritis had a total of twenty-two pregnancies following the original one with pyelonephritis. The interval between pregnancies varied from one to five years, with an average of three years.

The importance of a cure of the urinary infection either during pregnancy or in the interval be

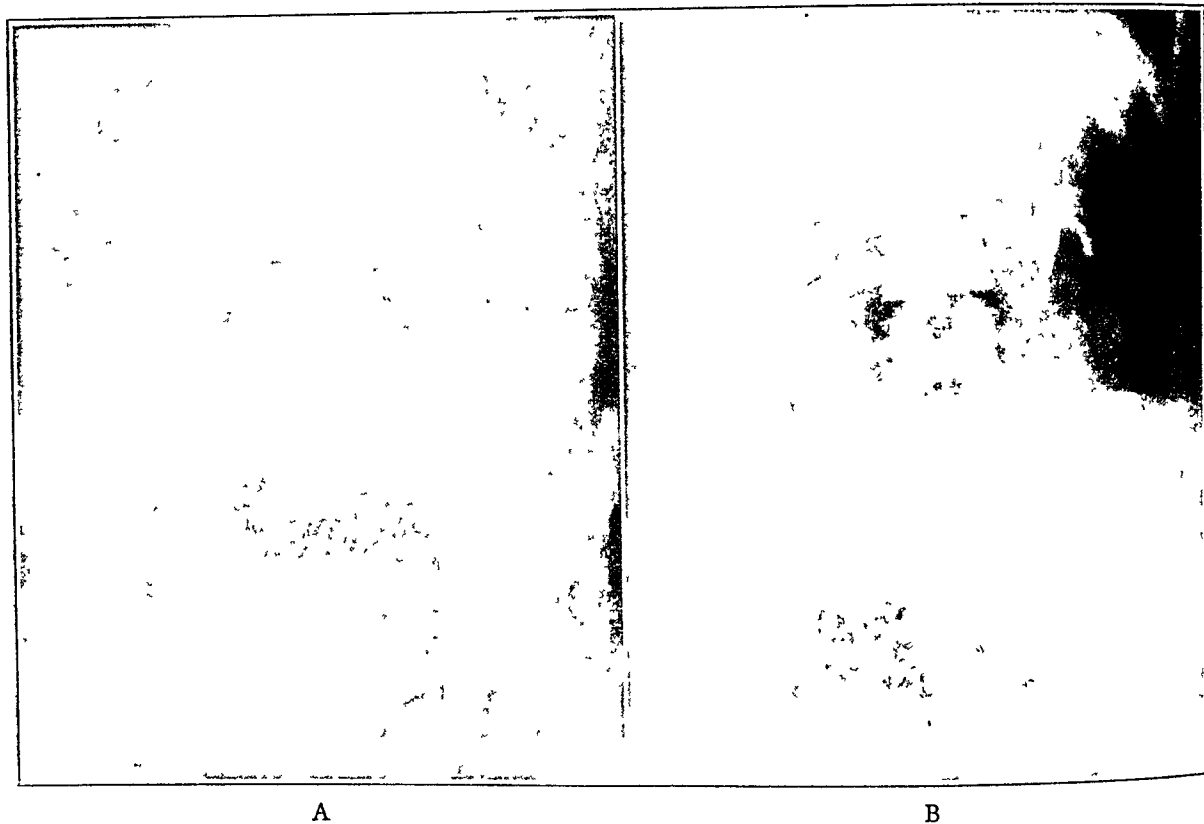


FIGURE 2.

*This patient, a primipara, had a right pyelonephritis during the sixth month of pregnancy. A shows the typical pyelographic changes in the upper urinary tracts. B, taken nine months later, shows considerable resolution of the hydronephrosis and hydrometer.*

cent. Cystoscopic diagnoses were made in 34 patients.

Studies of renal function were not done routinely at the time of the first observations. The blood chemical findings, which of course did not measure slight changes in renal function, were normal in 40 cases.

This brief summary of the clinical data involving the initial attack offers nothing new on the subject, but the following material, which shows the course of events when the patients returned in a subsequent pregnancy, is of interest. In approximately 65 per cent, the subsequent pregnancy was normal, with no clinical evidence of pyelonephritis. Seventeen patients, or 23 per cent, de-

tween pregnancies has been emphasized repeatedly.<sup>1,2</sup> Likewise, careful examination of a catheter specimen of urine by stained sediment or culture has been stressed as essential in determining cure. Data from this series of cases support both contentions. Of 43 patients in whom a sterile urine was obtained post partum following their initial pyelonephritis of pregnancy, 8, or 19 per cent, developed pyelonephritis in a subsequent pregnancy. Of 36 patients whose urine was either still infected or unreported during the interval between pregnancies, 14, or 42 per cent, developed pyelonephritis in a subsequent pregnancy. (The total of 79 patients, instead of 72, is conditioned by the fact that a few patients had both a subse-

quent normal pregnancy and one complicated by pyelonephritis.) If one assumes that at least some of the patients whose urine was unreported probably had a sterile urine between the interval of pregnancies, the rate of recurrence of pyelonephritis in women who begin their pregnancy with an infected urine would be even greater than the 42 per cent just quoted.

Thus, a woman who has had pyelonephritis associated with pregnancy appears to have about one chance in four or five of developing pyelonephritis during a later pregnancy. The likelihood that pyelonephritis will recur during a later pregnancy, however, is greatly increased if she enters the succeeding pregnancy with an infected urine. Entering pregnancy with a latent or chronic pyelonephritis, she has only one chance in two of avoiding a febrile attack; if the pyelonephritis has been cured during the interval between pregnancies, the chance of her having a febrile attack is reduced to less than one in five.

Pyelographic data were obtained in 55 patients, in 29 of whom cystoscopy and retrograde pyelography were performed. Intravenous pyelography was used in the remaining 26. Two illustrations of the pyelographic studies are instructive. Figure 1 illustrates delayed secretion of the intravenous dye by the right kidney during two pregnancies three years apart, each of which was complicated by right pyelonephritis. It is interesting to observe the same degree of ureteral dilatation in the two pregnancies even though the position of the fetal spine is reversed. Figure 2 illustrates the degree of anatomic recovery that may take place following pregnancy.

To demonstrate the relation of hypertension to pyelonephritis, we have noted the blood pressure readings from the charts of 17 patients who had recurrent pyelonephritis (Table 1). Although the

average interval between pregnancies was not unusually long, there appears to be no tendency toward hypertension during a succeeding pregnancy

TABLE 1. *Blood Pressures in Patients with Recurrent Attacks of Pyelonephritis of Pregnancy.*

CASE NO.	FIRST ATTACK		SUBSEQUENT ATTACK	
	YEAR	BLOOD PRESSURE mm Hg	YEAR	BLOOD PRESSURE mm Hg.
5	1934	114/60	1938	110/70
7	1936	116/68	1939	???
8	1936	133/88	1938	158/109 to 127/78
11	1931	120/70	1936	110/70
12	1935	110/64	1937	112/88
16	1934	120/70	1936	114/64
17	1934	110/60	1938	112/80
20	1934	114/60	1938	110/70
21	1934	140/86	1938	128/80
25	1934	112/68	1936	118/90
26	1935	106/68	1937	110/80 to 103/90
28	1935	100/58	1939	118/60
31	1931	118/70	1936	???
33	1936	110/70	1938	100/58
34	1937	112/80	1939	128/80
35	1934	136/90	1937	104/72
37	1934	150/88	1938	128/80

as the result of pyelonephritis during a former pregnancy.

#### SUMMARY

In a series of 72 patients, recurrent pyelonephritis of pregnancy had an incidence of 23 per cent. If the urine becomes sterile during the interval between pregnancies, the chance of recurrent pyelonephritis is less than one in five, and if the urine remains infected, the chance is about one in two.

There appears to be no tendency toward hypertension during a succeeding pregnancy as the result of pyelonephritis during a previous pregnancy.

#### REFERENCES

- Crabtree, E. G., and Prather, G. C. Urinary tract infections associated with pregnancy. *J. A. M. A.* 101 1928 1933, 1933.
- Crabtree, E. G., Prather, G. C., and Fries, E. L. End results of urinary tract infections associated with pregnancy. *Am J Obst & Gynec* 34 405-419, 1937.

## THE GOVERNOR'S ADDRESS\*

ROBERT O. BLOOD, M.D.

CONCORD, NEW HAMPSHIRE

**T**HE participation of the state in the practice of medicine, from both the physician's and the state's point of view, extends over the last hundred and fifty years. I propose to deal with the incidents and developments that have shaped our present-day state health program, the relation between the state medical profession and expanding government control, and subsidy of state health.

The New Hampshire Medical Society is closely associated with early efforts to promote state responsibility for common health conditions. Following its incorporation by the legislature in 1791, the Society promoted standards for physicians, an action that shows clearly its concern for public health and welfare. Numerous later acts of the Society indicate its concern with the public at large. In this respect, and proudly, it was the forerunner of an organized public-health agency. Sensitive to its responsibility to New Hampshire citizens, the Society adopted the following two resolutions in 1824:

RESOLVED, That the practice of depositing medicines in stores, taverns and grog-shops, with directions to the common people for their use, is not only pernicious to the health and morals of society, but derogatory to the character and reputation of the physicians.

RESOLVED, That we disapprove the encouragement held out to the public through the medium of pompous advertisements, that the daily use of bitters is conducive to health; and we consider the facility with which Stoughton's Elix. Spec., bitters etc. may be secured at country stores, one of the most direct means of inducing habits of intemperance (the bane of society) of any within our knowledge.

Early in the nineteenth century, the Society attempted to establish a medical school in Concord, hoping to elevate the standards of professional public-health guardians. The Society's bitter struggle to protect the community from the inducements of the infamous Concord Botanic Infirmary is another indication that it was not passive in armoring the community against the invasion of a medical hoax.

The Society agitated early for control of vital statistics by the State. In 1848, it appointed a committee to study the problems relating to birth and death registration, and to bring the issue before the legislature.

In 1868, Dr. Granville P. Conn, a man whom I knew as an able physician and energetic leader in the early field of public health, joined the committee of the Society. Not at once successful in putting through state legislation, he cut through the jungle of indifference, ignorance and tradition. Indirectly prodding the State by initiating local ordinances, he finally succeeded with similar state legislation, but not for a decade.

The New Hampshire Medical Society entered the campaign for a state board of health largely as the result of an address delivered in 1872 by a Californian, Dr. Thomas M. Logan. Speaking as a realist, from experience gained in California's campaign for similar action, Dr. Logan outlined the duties of a state board of health as follows:

To create an interest in our work among the lay as well as the professional public. . . .

To raise up friends in all parts of the state to co-operate with us in our investigations in gathering sanitary information and in spreading it abroad. . . .

To encourage the formation of local boards of health, the registration of births, deaths and marriages, whereby mortality and other reports touching the vital condition of the people may be obtained.

Dr. Logan, like New Hampshire's Dr. Conn and others in the nation, was more than a diagnostician of bodily ills. He was an economist, a statesman and a prophet—all these, because he envisioned the broad economic and human influence of a sound program of state health regulation.

Dr. Conn, in the enthusiastic wake of Dr. Logan's appeal, was assigned to draft a bill for a state board of health and to secure its passage. Toward that end, he labored for a decade. He visited, he lectured, he taught, he influenced. For ten years, he carried on with prodigious energy, creating and sustaining interest in his public-health ideal. The records of the Society are marked during this period with efforts to create a state board of health. Since it is material available to all in the published reports of these years, I shall not deal with it. In the year prior to the passage of the act creating the board, the president of the Society wrote in his annual address:

A physician is often considered as a kind of fire extinguisher, to be sent for in time of conflagration, but as rather a useless member of the body politic when there is no actual crisis. To think this way is to wholly misunderstand the work of the professions. . . . The physician should have the same pre-

\*An address delivered by the Governor of New Hampshire at the one hundred and fiftieth Anniversary Dinner of the New Hampshire Medical Society, Manchester, May 14, 1941.

rogative in the state as in the family, and no man can be properly said to be a conscientious physician who does not, if allowed, have a general, vigilant, but not impertinent oversight of the hygienic arrangements of the household of which he is the sanitary inspector and adviser.

In 1881, the state legislature created a state board of health. Dr. Conn, exultant in his success, was at once appointed to the Board.

The Board of Health, under the terms of the act, was to consist of four appointees: three physicians and a civil engineer. It was granted license to elect its officers and to institute rules necessary to guard against epidemics or contagious disease, to be dispensed to citizens without cost. Cognizance was taken of sanitation in public buildings. Vital statistics were taken over by the Board. Local boards were to be assisted and advised; conditions in localities were to be investigated. That the people of the State should be served was pre-eminent in the writing of the act.

Examination of public-health legislation in New Hampshire is a study in itself. In 1892, all State Board of Health regulations were made enforceable by an act that made their violation punishable by fine. Also in 1899, the practice of embalming was brought under regulation, and thus the Board's authoritative arm stretched into a new orbit. In 1901, the Board was "authorized to establish and equip a laboratory . . . for the chemical and bacteriological examination of water supplies, milk, food products and drugs; and the investigation of cases and suspected cases of diphtheria, typhoid fever, tuberculosis, pneumonia, malaria glands and other infectious and contagious diseases." A chemist was to make investigations and analyses of public water supplies and of foods and drinks offered for sale in markets, to discover adulterated and fraudulent products. A quarterly bulletin was to be published. Moreover, all investigations by the Board were to be made free to the people of the State. In the same year, vital statistics were indexed by law. The following year, an act provided for the restriction of communicable diseases. The procedures familiar to all physicians today were made law: quarantine, case reporting to local and state boards of health, placarding of quarantine premises and disinfection of infected premises.

In 1903, the legislature passed an act to enable the State Board of Health to prevent the furnishing of contaminated water for domestic consumption, and in the same year gave the superior court jurisdiction in equity to enforce the orders of the Board. The session of 1907 was successful in pure-food legislation, with an act preventing the manufacture or sale of adulterated or misbranded

or poisonous foods, drugs, medicine and liquors. In this, the Board was to assume regulatory supervisory powers.

At the next session, the powers of the Board were further extended by an act providing for the establishment of dispensaries for the detection and treatment of tuberculosis. In the same year, supervisory power was given the State Board of Health over the manufacture and sale of cocaine products. Other legislation in 1909 provided for sanitary inspectors, embracing the examination of meats and general food products and of local sanitary conditions.

As an extension of the tuberculosis clinics and in an effort to check the spread of the disease, the Board was charged, in 1911, with the registration of all cases. The same year was also marked by its authority to enter and inspect establishments producing or selling food. With an act relating to child labor, the State Board of Health entered the province of public-welfare work, for the act authorized the regulation of child labor by the staff. Later, the Board assumed control of communicable diseases in unincorporated districts; thus, it acknowledged responsibility for the health of those in the rural areas of the State. For many years, members of the medical and nursing professions had campaigned for legislation to cover the care of inflammation of the eyes in the newborn—ophthalmia neonatorum. The Board was authorized to make regulations designed to prevent this disease. Furthermore, an act was passed to provide for certified and inspected milk.

During the next three sessions of the state legislature, medical inspection of schools was made compulsory, as was the formal reporting of occupational diseases. Regulations were made dealing with the discharge of sewage into streams, and providing for the construction and enlargement of public water systems. The control of the Board over infantile eye diseases was increased, and the distribution of antitoxins was provided for. The Board was also authorized to govern the sanitation of schoolhouses and to examine their teachers and janitors for communicable diseases, and power was given to license and inspect private asylums and sanitariums.

The trend during these first thirty-nine years is obvious. More than a trend, it is a lively and colorful pageant of human betterment. The demand for the services of the State Board of Health increased. Each session of the legislature witnessed the passing of additional laws, added health burdens being placed on the staff of the Board. It has been a consistent rise—even to the present day. This historical development of New Hamp-

shire's Board of Health led to the broad program in effect today.

Increased responsibility and added functions were accompanied, inevitably, by a mounting health budget. Always, leading to the battle front of progressive government, there must be a pipeline of monetary supply. It must be maintained; it must be guarded; and even more important, it must be regulated. That is the strategy of "good government." There is, however, an interesting balance between function and cost. This is evident regarding the activities of the Board of Health in New Hampshire.

Under the terms of the original statute of 1882, the total cost of the Board's operation was not to exceed \$3,000 in any year—a calculation that was both naïve and optimistic; it suggests the man who makes his "down payment" and walks away with the inflated pride of full ownership. Actually, the operation of the Board during the next year approached the \$5,000 mark, and by 1886, the total annual expenditure was well over \$8,000. The following years, up to the turn of the century, averaged between \$4,000 and \$7,000. In 1902, the year in which the Laboratory of Hygiene went into operation, the cost of the Board rose to more than \$14,500. This was a high level for the decade that followed. In 1913, because of the salaries of chemists, bacteriologists and sanitary inspectors and the cost of vital statistics, the budget expenditures increased to more than \$16,000. This level was maintained, more or less, until 1920, when the total expenditure of the board reached \$27,000. Five years later, this figure was shadowed by a total expenditure of more than \$70,000, a cost very nearly repeated in 1930.

The initial federal grant-in-aid for state health activities came in 1936, when the State availed itself of \$8,423. In the same year, the State contributed, in addition, \$73,671. From \$8,000 in 1936, federal money expended for health purposes rose in 1937 to \$52,000, and to more than \$83,000 in 1938. In the latter year, the state appropriation and expenditures exceeded this amount, bringing the cost of public-health functions in the State to more than \$167,000. The federal grant in 1939 rose to more than \$100,000; this was matched by state funds of \$95,000. In 1940, the last full year available, federal and state expenditures totaled almost \$205,000. These five years, 1936 through 1940, have witnessed a total expenditure of more than \$362,000 in federal funds, matched by \$410,000 in money contributed by the State, an aggregate expenditure on state public health of nearly \$772,000. Dr. Conn. who asked for a few hundred dollars for birth and death registration, would have been startled at these figures.

The annals of individual achievement are no more praiseworthy in any section of the country than in New Hampshire among the members of the medical profession, who toiled long and arduously for the gains we count today; moreover, they often toiled without adequate clinical and surgical equipment. They were men who generously subordinated their own comfort to communal welfare. They were familiar with the long journeys to hillside homes. Often, they were deprived of the nourishment of sleep when the wheel of rest was suddenly halted by a neighbor-messenger. In their time, they were the claim adjusters of human affairs, assuaging malice, greed and misunderstanding. They sat through the long nights to listen to the caricature of men's lives as it sifted through the veil of half-consciousness. In many respects the first citizens of the State, they were welcomed to the great aristocratic residences and hailed in the remote, silent reaches of the northern logging roads. With scant knowledge of many medical subjects now commonplace, they often resorted to desperate means in saving human life—and with incredible success. A stalwart lot, whose business was rooted deep in human behavior, they frequently applied the anesthetic of prudence when skill was lacking. They were the first proponents of collective and organized public health. For they were the itinerant teachers of elementary hygiene in the home. Whereas today a relatively complicated scheme operates, they once gave generously of their efforts, sometimes ushering in new life, six miles from home, for the "munificent fee of fifty cents." We have increased our mastery over time and space. We have organized our individual experience and resources in a state board of health. These are distinct advances, but in many respects, earlier men were the conquerors of problems more formidable than those of the present day.

New Hampshire is spending heavily on public-health projects. The burden of this to the taxpayer has a significance that cannot be discussed here. The increasingly heavy outlays are also, I am convinced, of vital consequence to physicians in the State. The medical profession is one of the few individual careers left. Increasing governmental participation will standardize the performance of professional men engaged in medical practice. Although the average level may be slightly raised, the medical "artist" will be reduced to uniform work. Increased subsidy means greater uniformity and the loss of the great men of medical science. That, briefly, is the case for the profession itself.

There is also a case for the people of the State, particularly the needy sick. If the sponsors of government-regulated medicine are earnest in their

endorsement of adequate medical care, they will see to it that such care is rendered by professionally competent men; it cannot be provided in any other way. The citizens should be cautious in estimating the ability of legislated medicine to provide competent medical care for the needy, just as careful as they should be in protecting themselves from the advice and treatment of nonmedical practitioners. There is grave doubt whether any body politic can properly assess the needs of the indigent sick. Such action must be left in the hands of the medical profession. The welfare of the sick will be best preserved by continuation of the traditional principle of allowing the patient to choose his physician. That right must be maintained, unless the patient is judged incapable of making the selection. The underlying value of this prerogative is well understood by the medical profession, although often regarded casually by governmental health, welfare and relief administrators.

What is the answer? Must we cease altogether to accept governmental aid in our health program? And, if we do, what is to become of the organization already in motion? I do not believe that we need ignore the aid offered our state units. To do this would be to renounce the obligation of delivering scientific medical care to the people, whether they can afford it or not. No one in the profession is tolerant of that attitude, and if he were, the profession would not long remain tolerant of him. The State Board of Health, like other welfare and relief agencies, must be main-

tained to meet the demands that education is prompting the people to make. We cannot educate the citizenry to better health and then withhold it from them. The solution rests, I am convinced, with the medical profession itself. A successful program must keep in mind three essential functions: preventive medicine, curative treatment and the care of those chronically ill.

\* \* \*

Thus, from the earliest times there has been a constant demand for increasing state participation in the regulatory controls of the State Board of Health. With this extended control has come a constant demand for ever increasing amounts of money to perform these functions, the State has met these demands. In general, the requests have come from the medical group and not from the layman. Of course, the money to pay these bills comes, in the final analysis, from the taxpayers. With the growing financial participation of governmental units has come increased control over the functions of public health. This privilege has been claimed on two arguments: that it is economical, and that the organization, or people furnishing the money, has a right to dictate its use. In these days, when the medical profession is rightly opposing state medicine and increased regulations of its practice, I believe that physicians should weigh carefully the advisability of asking for additional governmental participation, lest we receive, in its wake, the state regulation of the practice of medicine.

PERINEAL PHLEGMON\*

S. RICHARD MUELLNER, M.D.†

BOSTON

THIS paper is based on a study of 36 cases of perineal phlegmon treated at the Boston City Hospital during the last ten years.

Perineal phlegmon, or periurethral gangrene, is referred to as "extravasation of urine" in the older textbooks of urology. It was observation of cases of this disorder that led Colles<sup>1</sup> to the discovery of the superficial perineal fascia; he believed that extravasating urine was confined to the superficial perineal pouch by the anatomic attachments of the fascia, which he described in 1811. So-called "urinary extravasation," or perineal phlegmon, was at that time considered to be due to seepage of urine into the tissues through a tear in the urethra proximal to a stricture. One can readily understand the logic of this concept, since it stems from an era when little was known about bacteria or the chemistry of urine, and the identification of the fluid in the tissues depended entirely on the senses of sight and smell.

In recent years, this mechanistic view of the etiology of perineal phlegmon has been discarded by many. French urologists have claimed for years that perineal phlegmon is due to an infection by anaerobic bacteria.<sup>2</sup> Keyes and McLellan,<sup>3</sup> Herman<sup>4</sup> and Keyes and Ferguson<sup>5</sup> agree with this concept and assert that urine is never found in the tissues of the perineum, scrotum, penis and abdominal wall in cases of perineal phlegmon.

However, some writers on this subject still hold to the old view of urinary extravasation in spite of considerable evidence against such a belief.<sup>6-10</sup> Briefly, this evidence is as follows: lacerations of the urethra through which the seepage of urine might be expected to occur are rarely, if ever, demonstrable at operation; collections of fluid in the tissues have been seen to occur distal to a stricture of the urethra<sup>11</sup>; stricture of the urethra is often absent (Table 1); a comparison of the urea content of the fluid in the tissues and of the bladder urine shows that the former is definitely not urine<sup>5</sup>; and injection of sterile urine into the tissues of experimental animals has failed to reproduce the syndrome of perineal phlegmon.<sup>12, 13</sup>

\*Presented at a meeting of the New England Section of the American Urological Association, Boston, April 24, 1941.

†Instructor in urology, Tufts College Medical School; assistant visiting urologist, Boston City Hospital; junior visiting urologist, Beth Israel Hospital.

That the fluid in the tissues was definitely not urine, was easily proved in 3 of the 36 cases observed in this study. In these patients, the fluid in the subcutaneous tissues was watery, and contained aerobic and anaerobic bacteria, whereas the bladder urine was concentrated, clear and sterile.

A significant matter, which has not been stressed before, is the role of the lymphatic channels that drain the membranous and bulbous urethra, as well

TABLE 1. Incidences of Urethral Stricture and of Urinary Infection in Cases of Perineal Phlegmon.

CONDITION OF URETHRA		BLADDER URINE AT OPERATION	
	PERCENTAGE OF CASES		PERCENTAGE OF CASES
Small-caliber stricture (impassable) . . . . .	53	Infected . . . . .	59
Large-caliber stricture (passable to No. 16 to 20 Fr. catheter) . . . . .	22	Mildly infected (5 to 10 white blood cells per high-power field) . . . . .	11
Normal lumen . . . . .	25	Sterile . . . . .	39

as the perineum, scrotum, penis and lower abdominal wall. These lymphatics, interestingly enough, follow accurately the outlines of Colles's fascia.<sup>14-16</sup> Individual variation in the course of the lymphatics, moreover, is not uncommon, and such variations may well account for the surprising spread of the phlegmon beyond the confines of Colles's fascia. Thus, in 2 of the cases in this series, the infection extended to the thighs, and in 5, a great deal of fluid was found in the pre-vesical space at cystotomy. Extension of the inflammatory reaction to the axillas and buttocks has been recorded in the literature.<sup>2</sup>

The clinical picture of perineal phlegmon is briefly as follows. The onset of the infection is often marked by chills and fever, followed by pain and swelling of the perineum and accompanied by increasing difficulty in voiding. In some cases, a long history suggestive of stricture of the urethra precedes the onset of the illness. The perineal swelling quickly spreads to include the scrotum, penis and abdominal wall. On examination, the patient is feverish and toxic, even comatose. The pulse is rapid and weak. The bladder is readily felt suprapubically, the hypogastric area is swollen, the penis and scrotum are often enormous, and the perineum bulges extensively.

The diagnosis of perineal phlegmon is readily made on the basis of the history and physical

findings In the differential diagnosis, periurethral abscess or an ischioirectal abscess pointing in the perineum must be excluded The following cases illustrate some of the typical features of the condition

### CASE REPORTS

CASE 1 B M, a 49 year-old Negro, entered the hospital because of swelling of the penis and scrotum of 74 hours duration He had had gonorrhea 13 years before entry this had been treated by self-medication Since then symptoms suggestive of stricture of the urethra had been present On the day before admission the patient noticed soreness in the perineum, followed by a local swelling which rapidly extended to the scrotum and penis and was accompanied by retention of urine, fever and malaise

On examination the patient was feverish and in distress The bladder was palpable at the level of the umbilicus There was a swelling over the hypogastrium and the penis and scrotum were enormously swollen, red and edematous

At operation an impassable obstruction was found in the urethra 8 cm from the meatus Through a median perineal incision the subcutaneous tissues were found to be very edematous The edema fluid was colorless and of fecid odor, and the culture yielded a beta hemolytic streptococcus and *Staph aureus* The perineal incision was undermined and connected by rubber tissue, with counterincisions in the groins scrotum and penis The bulb and the urethra were explored and were found to be intact but very cyanotic, with engorged veins on their surfaces A perineal urethrotomy was performed A No 20 catheter passed easily into the bladder Clear urine-colored urine, which was later found to be sterile and pus free, was obtained from the bladder

The postoperative course was very satisfactory On the 26th day after operation the urethra was readily dilated with bougies and sounds The patient was discharged 5 weeks after admission the wounds were healed and he was able to void a good stream

CASE 2 W M, a 67 year old man, was admitted because of swelling of the genitalia and retention of urine Two weeks before entry the patient noticed swelling of the penis and scrotum, in addition to inability to void He had had gonorrhea many years previously, but had no symptoms of stricture of the urethra

On admission the patient was stuporous and very dehydrated The bladder was palpable below the umbilicus The suprapubic area was swollen, and the skin was red and blistered The penis and scrotum were enlarged to three times their normal size The perineum was bulging and red, and the inflammatory reaction extended over the buttocks

The operative procedure was essentially the same as that in Case 1, except that the bladder was drained by cystostomy The prevesical space was edematous The bladder contained concentrated sterile urine In the perineum, the subcutaneous tissues were gangrenous and bathed in foul pus, which on culture yielded an alpha hemolytic streptococcus, *Staph aureus* and an enterococcus The urethra and the bulb were intact, but the urethral mucous membrane consisted of gray slough, so that the urethral lumen was obliterated When an attempt was made to pass a bougie into the urethra, the instrument stuck in the meshes of the slough, which was of a gritty consistence Postoperatively, sulfathiazole was used as an adjunct to combat the infection

The convalescence was uneventful It was remarkable that the urethral lumen became reestablished at the time of the patient's discharge from the hospital

CASE 3 J M, a 51 year-old man, was extremely toxic and comatose at the time of entry He was said to have had swelling of the genitalia and difficulty in voiding for the previous 2 weeks

The temperature was 104°F, and the pulse 120 weak and thready The bladder was not palpable The hypogastrium was swollen, red and blistered, and red streaks extended to the upper abdomen and over the thighs The genitalia were greatly swollen the perineum bulged, and the buttocks were red, blistered and indurated

The operative procedure was the same as that in Cases 1 and 2 The subcutaneous tissues were edematous and sloughing On culture an alpha hemolytic streptococcus and a fusiform bacillus were found The urethra and the bulb were intact, but the urethral mucous membrane was black and sloughing obliterating the urethral lumen, in a manner similar to that in Case 2 The bladder contained about 180 cc of uninfected, concentrated urine

Postoperatively, and without regaining consciousness, the patient developed signs of bronchopneumonia and died days later

### DISCUSSION

These case reports bring out a few points that merit emphasis Colles's fascia was no barrier to the spread of the pathologic process Moreover, the urine in each case was concentrated and sterile, yet the fluid in the subcutaneous tissues was watery

TABLE 2 Analysis of Cases of Perineal Phlegmon, Showing Mortality Morbidity and Age Distribution

Mortality	3 per cent
Morbidity	
Average 1 hosp al stay	44 days
Longest hosp stay	94 days
Shortest hosp al stay	12 days
Age	
Average	55 years
Oldest	7 years
Youngest	26 years

and foul and harbored various aerobic and an aerobic bacteria Laceration of the urethra was not demonstrable Finally, the urethral mucous membrane in Cases 2 and 3 was gangrenous and sloughing, and thus produced an obliterated lumen The passage of an instrument through such a urethra could easily give the erroneous impression that a stricture existed

The prognosis of perineal phlegmon is grave The morbidity is high, and the mortality has remained at about 40 per cent (Table 2)<sup>1</sup> The high mortality is partly due to the age and the debility of the patient with this lesion, and partly to the high virulence of the infection in certain patients Although delay in making a diagnosis and beginning treatment obviously adds to the seriousness of the outcome, prompt action does not always prevent death (Table 3) Of 11 patients in the same age group, who were treated



in a similar manner during the first three days of the disease, 6 survived and 5 died.

The management of perineal phlegmon is based on three principles: treatment of the infection; relief of the retention of urine; and treatment of the urethral stricture.

Prompt and adequate surgical drainage, with thorough decompression of the distended tissues, is the paramount factor. This can be accomplished by long, free incisions, or by multiple

TABLE 3. *Relation between Preoperative Duration of Perineal Phlegmon and Postoperative Mortality.*

DURATION OF ILLNESS <i>days</i>	NO. OF SURVIVALS	NO. OF DEATHS
1-2	6	5
3-6	7	2
7-14	3	2

incisions, widely undermined, and connected by rubber tissue. I prefer the latter method, because, if it is properly executed, satisfactory drainage and decompression result and healing is more rapid, with less scarring and deformity.

Chemotherapy, based on accurate bacteriologic and renal-function studies, is a valuable therapeutic adjunct. Zinc peroxide dressings, the local application of sulfanilamide powder and irrigation of the wounds with Dakin's solution are also useful.

The retention of urine is best relieved by cystotomy, particularly if dense strictures of the urethra are present or if the urethral mucous membrane is gangrenous and sloughing. It is amazing how rapidly such a urethra regenerates if it is not unduly traumatized. Bladder drainage may be established by perineal urethrotomy if the urethra is strictured and no slough is present or by penile catheter if the urethra is intact. The stricture of the urethra can be dilated or incised, if the patient's condition permits, or treatment can be postponed till a later date.

#### SUMMARY AND CONCLUSIONS

The literature on perineal phlegmon is reviewed, and an analysis of 36 cases is presented. Three cases are described in detail.

Perineal phlegmon is an infectious process and is not due to "extravasation of urine" into the tissues confined by Colles's fascia. The anatomic attachments of this fascia do not prevent the spread of the infection.

Stricture of the urethra and pyuria are often absent. A sloughing urethral mucous membrane, moreover, may mislead one into believing that stricture exists.

Smears and culture of the pus in the subcutaneous tissues, as well as blood cultures and renal-function studies, are necessary for successful chemotherapy and for a better understanding of the pathology of this disease.

Adequate surgical drainage, with decompression of the distended tissues, is imperative. Depending on the condition of the urethra, the retention of urine can be relieved by penile catheter, by perineal urethrotomy or by cystotomy.

520 Beacon Street

#### REFERENCES

- Colles, A. *A Treatise on Surgical Anatomy*, 219 pp. Dublin: Gilbert and Hodges, 1811.
- Gayet, R. Considérations sur la thérapeutique et les résultats opératoires des phlegmons diffus gangréneux du périnée. *Lyon chir.* 36:661-674, 1940.
- Keyes, E. L., and McLellan, A. Stricture of the urethra. In *Cabot's Modern Urology*. Vol. I. 951 pp. Philadelphia: Lea and Febiger, 1936. Pp. 375, 390.
- Herman, L. *The Practice of Urology*. 923 pp. Philadelphia and London: W. B. Saunders Co., 1938.
- Keyes, E. L., and Ferguson, R. S. *Urology*. Sixth edition. 707 pp. New York and London: D. Appleton-Century Co., 1936.
- Mullen, E. A. Extravasation of urine. *Pennsylvania M. J.* 42:770-774, 1939.
- Negley, J. C. Urinary extravasation. *California & West. Med.* 45:38-41, 1936.
- Ockerblad, N. F., and Carlson, H. E. Urethral urinary extravasation. *Surgery* 3:391-396, 1938.
- Ravenel, J. J. Extravasation from lower urinary tract. *J. Urol.* 40:126-134, 1938.
- Eisendrath, D. N., and Rolnick, H. C. Stricture of the urethra: complications. In *Urology*. Fourth edition. 1061 pp. Philadelphia: J. B. Lippincott Co., 1938. Pp. 233-237.
- Johnson, F. P. Periurethral abscess. In *Nelson New Loose-Leaf Surgery*. Vol. VI. New York: Thomas Nelson & Sons, 1940. Pp. 50-54.
- Bezza, P. L'infiltrazione urinosa dal punto di vista sperimentale. *Arch. ital. di chir.* 41:1-62, 1935.
- Wolfer, J. A. Urinary extravasation. *Surg., Gynec. & Obst.* 26:296-302, 1918.
- Nesselrodt, P. J. An anatomic restudy of the pelvic lymphatics. *Ann. Surg.* 104:905-916, 1936.
- Parker, A. E. The lymph vessels from the posterior urethra, their regional lymph nodes and relationships to the main posterior abdominal lymph channels. *J. Urol.* 36:538-557, 1936.
- Rouvière, H. *Anatomie des lymphatiques de l'homme*. 490 pp. Paris: Masson et Cie, 1932.
- Campbell, M. F. Periurethral phlegmon (urinary extravasation): a study of one hundred and thirty-five cases. *Surg., Gynec. & Obst.* 48:382-389, 1929.

## CLINICAL NOTE

SHAKING CHILLS IN  
TYPHOID FEVER\*

MARK AISNER, MD † AND LEO WAITZKIN, MD ‡

BOSTON

THE purpose of this report is to emphasize and to bring to the attention of clinicians the not uncommon presence of shaking chills in typhoid fever, either at the onset or during the course of the illness. The impression seems fairly well established in the minds of many physicians not only that chills are extremely rare but also that their presence in a given case militates against the diagnosis of typhoid fever. This concept is also found in many of the textbooks of medicine, whereas in others a very casual attitude is assumed concerning either the presence or absence of chills. The earlier writers on typhoid fever were well aware of the occurrence of chills, and one could not improve on a few excerpts taken from their writings. In an analysis of 303 cases of typhoid fever at the Massachusetts General Hospital from 1921 to 1835 Jackson<sup>1</sup> commented as follows:

In a very large proportion of cases chills occurred either at the commencement or late in the disease or both. It may not be useless, however to say that I do not find chills at an advanced or late period of the disease, to have been usually followed by very grave consequences though I had previously had a

of the onset of the disease. Now and again in the journals a case is reported in which chills have been a special feature, and the complication is spoken of as a manifestation of ague. He [Peabody] had also seen severe chills followed by elevation of temperature as a symptom of typhoid fever, which did not affect the subsequent course of the disease.

In the same report Osler classified chills in typhoid fever, and his classification and comments are worth repeating. Six categories were listed:

*Chills at the onset of the disease.* Seventy-nine cases were studied, 13 of which began with shaking chills. In 2 there were several severe rigors. Three patients had no chills, whereas the remaining 8 had single rigors.

*Chills at the onset of the relapse.* Two cases were described: the relapse in one having occurred on the sixty-fourth day of the illness and having been marked by several severe chills. In the other the relapse was ushered in by a severe single chill.

*Chills as a result of treatment.* Osler considered therapy to be the commonest cause of chills in typhoid fever, especially that following the use of antipyretics. A dose of 5 or 10 gr of antipyrine was sufficient to induce a chill in many patients. This observation was also noted by Janeway, whom Osler<sup>2</sup> quoted as follows:

If we give the modern antipyretics in large doses chills will occur, which are due simply to the fact that the temperature has been depressed and then it rises and this rise is accompanied by mild and sometimes by severe chills. Drop your antipyretics, and the chills disappear.

*Chills with the onset of complications.* A rigor may precede the development of any of the complications of typhoid fever. Among these, Osler listed pneumonia, pleurisy, acute otitis media, suppuration in the mesenteric

TABLE I Onset and Frequency of Chills in Patients with Typhoid Fever

CASE NO.	AGE	SEX	OCCURRENCE OF CHILLS	NO. OF CHILLS	COMMENT
1	21	F	First week	Single	
2	36	M	First week	Single	
3	22	F	First week	Two	Each chill followed by administration of 10 gr of acetylsalicylic acid
4	31	F	First and second weeks	Repeated	
5	35	M	First and second weeks	Repeated	
6	72	F	First, second and third weeks	Repeated	During third week the patient complained of pain in the right flank; there was dullness at the right base and basal rales were heard bilaterally
7	17	F	First and third weeks	Repeated	
8	39	F	Fourth week	Repeated	

different impression on this point. They are noted in 29 cases and only two of these were fatal in their termination.

Osler,<sup>2</sup> in his *Studies in Typhoid Fever* prepared at the Johns Hopkins Hospital and published in 1895, also recognized chills as part of the symptomatology of the disease.

In the systematic writers on typhoid fever scarcely a reference is found to chills, except as a symptom

of pyemic abscesses of the kidneys, perforation of the ileum or appendix and acute peritonitis. Chills were also noted in some cases of thrombosis of the femoral or saphenous veins. In rare cases they preceded the development of acute and fatal hyperpyrexia. On the whole, however, rigors were rarely present in the complications of typhoid fever.

*Chills (? septic) during convalescence in severe and protracted cases.* In a few cases, rigors were noted throughout the course of the fever, without any localizing symptoms or signs to account for them. Two cases were described in which severe chills occurred in the absence of any recognized complication. Both patients recovered.

*Chills due to concurrent malaria.* Osler considered this a very rare cause of chills in typhoid fever.

\*From the First and Third (Tufts) Medical Services, Boston City Hospital, and the Department of Medicine, Tufts College Medical School.

†Instructor in Medicine, Tufts College Medical School; physician in outpatient clinic, Boston City Hospital.

‡Formerly house physician, Boston City Hospital.

The significance of chills in typhoid fever was recently illustrated by a private patient who had repeated shaking chills during the first two weeks of his illness. We then became interested in the incidence of this symptom among patients with typhoid fever at the Boston City Hospital. A review of the cases from 1937 to 1939 inclusive showed that 7 of the 16 patients had had one or more frank chills, an incidence in this small series of 44 per cent. The time of onset and the frequency of the chills in these 7 cases, as well as in the 1 in private practice, are shown in Table 1.

It will be seen that 2 patients had a single chill at the onset of their illness. In 1 case, chills were directly attributable to medication. In 1 case, repeated rigors were experienced during the first two weeks, and these continued throughout the third week, during which, however, evidences of complications were present. In the remaining 4 cases, repeated chills were noted, extending from the first to the fourth week after the onset of the disease. It is interesting to note that in Case 5, in which the patient had repeated rigors during the first two weeks of his illness, signs of pneumonia at the left base, by both physical and x-ray examinations, developed in the third week, during which chills were entirely absent. It may be pointed out that the cases presented can readily be catalogued according to Osler's classification.

## CONCLUSIONS

In the study of any disease, it is essential to appreciate not only the common symptoms but also those that occur less frequently. This is particularly so in illnesses, like typhoid fever, which require isolation and special precautions. It is for this reason that we have considered it useful to discuss the occurrence in typhoid fever of shaking chills, as distinct from mere chilly sensations, either at the onset or during the course of the disease, and to correct an unjustified impression that seems prevalent among members of the medical profession.

In conclusion, one may quote from McCrae,<sup>3</sup> who, in his chapter on typhoid fever, stated:

... For the student it is most essential to realize that the classical description of the disease does not fit every patient and this makes it so important that the disease should be studied from the patient and not from text-books alone. No symptom or sign is necessarily present, a point never learned by some men who refuse to make the diagnosis of typhoid fever unless certain classical features are found.

## REFERENCES

- 1 Jackson J. *A Report Founded on the Cases of Typhoid Fever, or the Common Continued Fever of New England, which Occurred in the Massachusetts General Hospital, from the Opening of that Institution in September, 1821, to the End of 1835.* 95 pp. Boston: Wright and Durrell 1838. P 42.
- 2 Osler, W. Chills in typhoid fever. In *Studies in Typhoid Fever* Extracted from *The Hospital Reports*. Vol. 4 and 5. 481 pp. Baltimore: Johns Hopkins Press, 1895. Pp. 445-457.
- 3 McCrae, T. Typhoid fever. In Osler and McCrae's *Modern Medicine: Its theory and practice*. Second edition. Vol. 1. 1093 pp. Philadelphia and New York: Lea & Febiger, 1913. Pp. 67-201.

## MEDICAL PROGRESS

### PSYCHIATRY: THE NEUROSES IN WAR

VERNON P. WILLIAMS, M.D.\*

BOSTON

IN considering the war neuroses, or what were labeled "shell shock" in the last war, the types and patterns of reaction do not differ from those encountered in peacetime, except in the precipitating factors. Of course, in war, more cases of such profound reactions as panic are seen. The experience of World War I gradually made it clear that emotional factors, fear of death, fear of and feelings of guilt about killing, conflict between duty and self-preservation, and so forth precipitated nervous disorders in soldiers, and that there was no tenable basis for considering physical injury to the nervous system, caused by shell explosions, responsible for the disorders.

Since, however, only certain men broke down nervously under the strain of war, there was a tendency in some quarters to regard the neurotic reactions as deriving essentially from cowardice, and consequently such reactions were sometimes treated summarily as weaknesses, requiring disciplinary action or at least disapproval. Considering the contagiousness of anxiety and hysteric reactions, when the general morale in a group is low, or when suggestibility runs high, there may well have been some justification and necessity for attempting to counteract them by disciplinary measures, particularly in acute situations that affected a group of men. There would be no more reason to treat the individual soldier by scolding and punishment than so to treat a civilian suffering with a neurotic disturbance.

Reprints of articles in this series are not available for distribution, but the articles will be published in book form. The current volume is *Medical Progress: Annual, 1940* (Springfield, Illinois: Charles C Thomas Company, 1941. \$4.00).

\*Assistant in psychiatry, Massachusetts General Hospital

Yet, even in the present war, the psychiatric point of view is not always the guiding principle. Bowlby and Soddy,<sup>1</sup> in a letter written to the *Lancet*, relate their experiences as psychiatrists in a war neurosis center, where they were supposed to treat the victims of the Dunkirk evacuation. They complain that they were not free to practice psychotherapy because the director of the center held that the men were not mentally ill but needed discipline and "somewhat forceful encouragement." This attitude is not the prevailing one however, in the English hospitals, as attested by the numerous papers on psychiatric treatment. The matter is mentioned simply because in time of war, more than ever, efficiency, stamina, reliability, hardness and perseverance are essential, and it is quite understandable that some of those who themselves may have these qualities and who see the imperative need of them may get "fed up" with being tolerant of or sympathetic with reactions that certainly spell weakness in relation to the job that must be done.

#### ETIOLOGY AND PROPHYLAXIS

The etiology of the neuroses in war is important, for it is related to the question of prophylaxis, especially as applied to the establishment of an armed force of emotionally or nervously stable men. Statistical data on neuropsychiatric disorders that developed in the United States Army during World War I show that in a large percentage of such disorders there had been a history of nervous or mental instability or neurologic defect long before the men affected entered military service.<sup>2</sup>

Much has been written to support the theory that evidence of personal predisposition and a family history of nervous instability are predominantly found in men who become the nervous invalids in military life. On the other hand, it is claimed that the heredity factor in the mass of neuroses and psychoses is but slightly more than that for healthy individuals.<sup>3</sup> Concerning predisposition, Wittkower and Spillane<sup>4</sup> write, "A majority of psychiatric authors believe that, given sufficient emotional stress, neurotic symptoms may appear in anyone, and that the existence of neurotic symptoms in civil life predisposes to their re appearance in an increased and altered form in war . . ."

Kardiner<sup>5</sup> boldly states that psychoneurosis of the usual type, hysteria or compulsion neurosis is decidedly not a contraindication to military service. He rules out "positively only men with a history of convulsions, tiqueurs, stammerers and men who have shown persistent disturbances of the autonomic nervous system over a long period,"

and adds that "these, however, can be inducted and assigned to noncombatant duties." He makes the well known observation that many persons who were severely neurotic and maladjusted in pre-military life adjusted themselves well to the military routine and lost their neurotic symptoms—"for the time being, at any rate." But it is also known that many men with histories of neurotic tendencies did not make good soldiers, and thousands of them, together with the men who temporarily lost their symptoms and who regained them later, have been supported by the Government ever since.

Thus, it is very much of a problem, and one that has no satisfactory solution, to decide who should be excluded from military service on neuropsychiatric grounds. However, there is fairly general agreement that a history of psychotic episodes, long standing and disabling neurotic reactions, drug addiction, chronic alcoholism and severe mental defect should debar a man from induction. Just what degree of mental defect will be the line between induction and rejection is not clearly defined, and seems to depend on the judgment of the particular induction board.

Since it is impossible to predict accurately what man with a neurotic background will break down under the stress and strain of service, it is often said that the neurotic person should not be rejected from service but should be placed in the proper type of service for his particular qualifications and limitations. How such an equitable and ideal distribution could be worked out has not yet been settled. However, Sutherland,<sup>6</sup> in England, writes: "A new scheme has been developed whereby it will be possible to have psychoneurotic soldiers placed in work suited to them and, if necessary, near their homes. This highly commendable innovation will be followed with much interest." So far, the United States Army has made no provision for using the man who is rejected for neuropsychiatric disability.

Numerous psychiatrists are skeptical of the wisdom of returning a man who has broken down to active service when he becomes symptom free. Too often, these men have broken down again.<sup>7, 8</sup>

#### TYPES OF REACTION

The reaction patterns seen more frequently in the present war, as in the last, are anxiety, depression and hysteria. Following the evacuation of Dunkirk, many acute neuroses, typified by marked exhaustion, extreme anxiety or panic, developed. Many of the men affected had definite previous histories of nervous stability. This suggests that men of fairly sound personality may suffer neurotic breaks if the strain is severe enough.

A description of the acute war neurosis is given by Sargant and Slater<sup>9</sup>:

The clinical picture was surprisingly uniform. There were first the signs of physical exhaustion — thin, fallen-in faces, pallid or sallow complexions. The expression and the whole attitude of the body was one either of tension and anxiety, or of a listless apathy. Neurological signs of a functional nature were usually present. A coarse irregular tremor of the hands was exceedingly common; in some cases it resembled the tremor of extrapyramidal lesions, and in one it presented the typical pill-rolling form seen in chronic encephalitis. . . . The resemblance to a parkinsonian picture was often increased by an immobile facies, and the superficial resemblance was so great that a number of cases had been sent here under a diagnosis of parkinsonism — i.e., they had been thought to be organic. . . . Reflexes were usually exaggerated, occasionally sluggish.

The mental symptoms were those associated with acute anxiety, including sleeplessness, terrifying dreams, a feeling of inner unrest and a tendency to be startled by the slightest noise. Amnesia, especially for the worst part of the past experiences, occurred in some cases, and additional hysterical symptoms in others.

In the present war, as in 1914-18, the incidence of psychotic developments is much smaller than that of the neurotic reactions.

#### PSYCHOPATHOLOGY

Although the literature on psychiatric subjects published to date relating to the present war is not extensive, some of the papers have included interpretations of the psychopathology of the war neuroses. It seems unnecessary to look very deeply into mental mechanisms to find a satisfactory explanation of the breakdowns that occur, since it is only reasonable that a certain number of soldiers will collapse nervously under the strain and terrors of war. Why one man, and not another, goes to pieces brings up the whole question of what constitutes nervous, emotional or psychobiologic stability. In war situations, the fundamental conflict is surely between the drive for preservation of self and the impossibility of honorable escape, or of escape at all. Of course, many other factors operate psychologically for the individual person.

Sutherland<sup>6</sup> notes "fear of death and an impotent rage against what were felt to be overwhelming odds," and adds, "This rage was often excited to a paralyzing degree by the slaughter of women and children or by the loss of friends."

The same writer, who considers a principal feature of the deeper psychology to be a basically insecure attitude toward the outside world, observes: "This attitude was manifested in many ways, particularly in the excessive dependence

upon those figures with whom security was felt — namely, their families. It was as though these men had always unconsciously dreaded the assertion of their independence as a dangerous aggressive process." Sutherland believes that the significance of the so-called "separation anxiety" — from home and family — cannot be minimized.

Slater et al.<sup>7</sup> write, "The experiences of war provide a stimulus to aggressive and sadistic impulses, with the consequence that guilt and its associated depressive affect are very common; or projection mechanisms may come into play, the man believing that every 'plane is coming specially to punish him.'"

The relation between aggressiveness and anxiety is also commented on by Wittkower and Spillane<sup>10</sup>:

During war . . . not only was the general taboo on aggressiveness and violence diminished but they were forced by military service into situations which inevitably stimulated their aggressiveness and hence provoked anxiety. This anxiety is a signal of a threatened breakdown of defences against aggressive impulses. If further stimulation of aggressive impulses took place, a complete breakdown ensued.

The same authors describe a psychoanalytic portrayal of the type of personality subject to developing neurosis in war, as follows:

. . . a basic personality structure characterized by self-centredness, over-conscientiousness, lack of sociability and lack of affection for relatives and friends. Such individuals suffer from the feeling that their personality has been neglected and that their importance is not sufficiently recognised. Many of these men were unable to carry out their tasks in practical life; others, capable of doing this, showed little initiative, however, or energy. . . . This group often showed an effeminate disposition, were dependent on their wives and frequently weakly potent. Life in the trenches exposed them to a danger of death which constituted a threat to their excessive self-love. Community life ran counter to their asocial tendencies, and the unconditional demand for self-sacrifice in war called for a renunciation of narcissistic privileges. More so than others, individuals of this type were prone to conflicts about aggressiveness, and, through their latent homosexual tendencies, the exclusive association with men constituted a special stress. Under such stresses these individuals increasingly regressed to a narcissistic level of development, leading to a state of infantile helplessness, with a complete surrender to their suffering, and a need to be pampered, cared-for and petted like children. The withdrawal of object libido (diminished capacity for external interests and emotional ties) results in an inflation of ego libido (self-centredness), which is expressed in abnormal hypochondriacal sensations and a further diminution of genital potency.

Miller<sup>11</sup> says that a person of the narcissistic type is terrified at the prospect of a wound, that he is likely to develop hysteric manifestations, fugues

and, sometimes, major mental disorders: "They cannot face the horrors of war, not because their bowels yearn for the slain, but because they identify themselves with every mutilation and death which the soldier has to witness"

The drastic changes effected in a man's life by being taken away from the accustomed routine of home and civic life, the necessity for adjusting to discipline and comradeship not of his own choosing, and inadequacies of personality in successfully meeting the required adjustments constitute enough strain in themselves to induce neurotic reactions in some men. Add to these or, if these difficulties are not present in a very plastic person, introduce an intermittent and recurring threat of death or injury, and it will require hardness of personality structure, an idealism or philosophy that makes one's own life unimportant or a strong masochistic or sadistic tendency to bring the soldier through without the development of neurotic symptoms.

The appearance of anxiety symptoms in the presence of such a situation as the Dunkirk evacuation does not, of course, necessarily presage the beginning of a neurotic break. Many men recovered completely from such symptoms after a few days of rest, quiet and adequate food.

#### TREATMENT

Psychiatrists generally agree, from experience in both the last and the present war, that quick, immediate treatment is imperative. If treatment is delayed, the symptoms and neurotic patterns tend to become set. Slater et al.<sup>7</sup> state, "Treatment of an acute neurosis is almost as urgent as that of the acute abdomen." Writing of cases that had become chronic, they remark:

Conversion symptoms had been allowed to persist, and large periods of amnesia had been left untouched. By the time they arrived for treatment here the neurotic reaction had become fixed. . . It is of the utmost importance that the acute neurotic should receive effective first aid as soon as he is seen.

If the patient shows evidence of marked fatigue or exhaustion, physical care is the first requisite. Such care should include rest, complete rest in bed, if necessary; sleep, with the aid of sedatives, if necessary; narcosis for several days, if the degree of anxiety requires it; and a full diet and large quantities of fluids. As pointed out by Sargant and Slater,<sup>9</sup> the narcosis has to be arranged, of course, so that the patient can receive adequate diet and fluids.

If hysterical symptoms or amnesia are present, they should receive consideration. In some cases, a thorough history taking, accompanied by per-

suation or suggestion, is enough to effect relief. Abreaction is recommended if any areas of amnesia remain. Hypnosis may be used. In some cases, the use of a narcotic intravenously has been substituted, and successfully, for hypnosis. Stungo<sup>12</sup> uses a 10 per cent solution of Evipan Sodium, and Slater et al.<sup>7</sup> have used sodium amytal.

Modified insulin therapy has been found to be of value in some cases of anxiety, hysteria and moderate depression, especially when there has been a loss of weight and physical depletion. In general Sargant and Craske<sup>13</sup> describe the technique, whose purpose is to induce light coma with insulin and to give heavy feedings with sugar and potatoes. The writers do not claim great success, but state:

Rapid gains in weight and improvement in appetite may often be obtained in neurotic subjects whose general physique has deteriorated under stress. Generalized neurotic anxiety, and hysterical and depressive symptoms in a reactive setting sometimes improve rapidly. The improvement is mainly in the associated symptoms of nervous exhaustion.

They point out, wisely, that a stable psychological recovery may well depend on restoration of normal physique.

In some of the war neuroses, there must be an inclination, whether or not entirely conscious, to cling to symptoms to prevent a return to duty. Slater et al.<sup>7</sup> suggest

the desire of the patient to evade further military service can be used to aid recovery rather than to perpetuate illness, he can be told, for instance, that he will be recommended for discharge, but only when he has recovered from his symptoms. A healthy civilian is of more value to the country than a sick soldier.

McLaughlin and Millar<sup>14</sup> describe the effective use of air-raid noises in psychotherapy. At first, rather crude apparatus was used to simulate the sounds of planes, dive bombing, machine-gun firing and so forth. Then with the help of the British Broadcasting Corporation, gramophone records of actual warfare were produced.

Though the procedure was intended to be a means of conditioning cases to noxious sounds, it soon became evident that it could be used as a speedy and practical method of abreacting patients. The process of letting a patient relive terrifying emotional experiences has a therapeutic effect. As a measure for producing abreaction the employment of war noises is much simpler than hypnosis or hypnarcosis. It is quick, effective, and does not demand too great technical skill. The patient is enabled to recall terrifying incidents which had determined his symptoms, and by expressing them in the secure atmosphere of the hospital his self control and confidence are helped.

McLaughlin and Millar report that a number of cases were helped by this method.

## CIVILIAN REACTIONS

Reports on civilian reactions to air raids and bombing in England indicate that genuine air-raid casualties have been much lower than might have been expected. The general opinion seems to be that bombing has precipitated breakdowns in persons who have been predisposed to nervous instability.

Atkin,<sup>15</sup> in writing of 300 consecutive admissions to a mental hospital, says that air raids were regarded as having a major influence in only 4 cases and were contributory in only 6. He contends that to assert a causal connection between an air raid and the development of symptoms is "as logical as to maintain that horses are a cause of phobia for these animals or that open spaces are the cause of agoraphobia. It is a common and well-known mechanism for anxiety or fear to be displaced from some repressed object or situation to any convenient symbol at hand."

Brown<sup>16</sup> writes:

The swarms of hysterics which were by some expected to follow bombing have not appeared, but nevertheless there are certain psychiatric disorders attributable to air raids. The symptoms in mild cases of shock are tremor, sometimes violent, dilated pupils, and tachycardia, with an emotional state of fear, perhaps mixed with anxiety about relatives and property. There is usually extreme sensitivity to noise and considerable restlessness. . . . Some cases . . . are in a limp semistuporous state, usually with a tremor. These patients are acutely scared and seem to be groping for hysterical symptoms to give them peace of mind and forgetfulness of the incident.

Brown has rarely found definite psychoneuroses in patients who previously had no neurotic traits, and in rare cases, the form has usually been some type of hysteric reaction.

Certain patients with long-established neuroses, such as obsessional states and complex-determined anxiety, have been little affected by bombing. Brown quotes one patient as saying, "Oh, I'm not worried about the bombs—it's this queer tickly feeling in the back of my head." A woman with obsessional fears of murder and suicide and knives said, "I'm afraid I can't get very concerned about

bombs; I wish I could—it would be more normal." Brown gives a reasonable interpretation of such reactions:

The extraordinary toughness of some well-established psychoneurotics to aerial bombardment may be due to the fact that they are to some extent reassured by seeing other people being as worried as they have felt for years. Another reason may be that the whole of their emotional tone and affect is concerned with their own problems, usually related to sexual difficulties, and there is no affect left for simple bodily fear. In some cases the urgency of the moment does serve to inhibit the patient's long-standing emotional conflicts, with resultant clinical improvement. In the Russian revolution it was said that the obsessional psychoneurosis became extinct. . . .

Psychoses may be precipitated by bombing, and air raids have apparently induced episodes of depression or mania in persons who were known to be subject to the manic-depressive psychosis.<sup>17</sup> Patients who have long been sick with psychoses, however, are not likely to be affected by air raids. Treatment of the civilian casualties is much the same as that for the men in service.

330 Dartmouth Street

## REFERENCES

1. Bowlby, J., and Soddy, K. Treatment of war neuroses. *Lancet* 2:343, 1940.
2. von Storch, T. J. C., Pratt, G. O., Farrell, M. J., Currier, D. E., and Viets, H. R. Observations and suggestions concerning neuropsychiatric examinations for the army of the United States. *New Eng. J. Med.* 224:690-697, 1941.
3. The Medical Department of the United States Army in the World War: Vol. X. *Neuropsychiatry*. 543 pp. Washington: Government Printing Office, 1929.
4. Wittkower, E., and Spillane, J. P. A survey of the literature of neuroses in war. In Miller, E. *The Neuroses in War*. 250 pp. New York: The Macmillan Co., 1940. P. 10.
5. Kardiner, A. The neuroses of war. *War Medicine* 1:219-226, 1941.
6. Sutherland, J. D. A survey of one hundred cases of war neuroses. *Brit. M. J.* 2:365-370, 1941.
7. Debenham, G., Hill, D., Sargent, W., and Slater, E. Treatment of war neurosis. *Lancet* 1:107-109, 1941.
8. Curran, D., and Mallinson, W. P. War-time psychiatry and economy in man-power. *Lancet* 2:738-743, 1940.
9. Sargent, W., and Slater, E. Acute war neuroses. *Lancet* 2:1, 1940.
10. Wittkower, E. and Spillane, J. P. 13.
11. Miller, E. Psychopathological theories of neuroses in wartime. *The Neuroses in War*. 250 pp. The Macmillan Co., 1940. P. 116.
12. Stungo, E. Evipan hypnosis in psychiatric outpatients. *Lancet* 1:507-509, 1941.
13. Sargent, W., and Craske, N. Modified insulin therapy in war neuroses. *Lancet* 2:212-214, 1941.
14. McLaughlin, F. L., and Millar, W. M. Employment of air-raid noises in psychotherapy. *Brit. M. J.* 2:158, 1941.
15. Atkin, I. Air-raid strain in mental-hospital admissions. *Lancet* 2:72-74, 1941.
16. Brown, F. Civilian psychiatric air-raid casualties. *Lancet* 1:686-691, 1941.
17. Harris, A. Psychiatric reactions of civilians in war-time. *Lancet* 2:152-155, 1941.

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTE-MORTEM AND POST-MORTEM RECORDS AS USED  
IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

### CASE 28081

#### PRESENTATION OF CASE

A twenty-three-year-old post-office clerk was admitted to the hospital because of intermittent pallor and weakness.

About eighteen months before entry, the patient became aware of pallor and slight general weakness. A local physician found the hemoglobin to be 35 per cent, and prescribed iron and liver-extract proprietaries. The patient improved for three or four months, and then relapsed soon after the discontinuance of the medicine. Another iron preparation was given by mouth, accompanied by injections of liver. At this time, the patient experienced a small amount of pain in the right side of his abdomen, occurring two to three hours after meals and relieved somewhat by defecation. About a year before entry, he consulted another clinic. Physical examination then revealed only pallor. Examination of the blood showed a red-cell count of 4,460,000 with 61 per cent hemoglobin, and a white-cell count of 7300. The red cells were hypochromic. The stools gave a strongly positive guaiac reaction on several examinations. Sigmoidoscopy and gastric analysis were both negative. Routine roentgen-ray examination of the gastrointestinal tract was negative; however, serial films with use of the Miller-Abbott technic finally showed a questionable polyp-like lesion near the cecum. When treatment was again stopped, the patient's hemoglobin fell to 48 per cent, rising again to 85 per cent with a red-cell count of 4,800,000 when iron therapy was reinstituted. The patient entered this hospital for an exploratory laparotomy.

On admission, the patient appeared husky, suntanned and well. There was a faint, blowing pulmonary systolic murmur. The heart, lungs and abdomen were otherwise normal.

The temperature, pulse and respirations were normal. The blood pressure was 114 systolic, 72 diastolic.

Examination of the blood showed a red-cell count of 5,450,000 with 15.5 gm. hemoglobin, and a white-cell count of 11,200 with 94 per cent polymorphonuclears. The blood Hinton reaction was negative. The urine was normal.

On the fifth hospital day, an operation was performed.

#### DIFFERENTIAL DIAGNOSIS

DR. THOMAS V. URMY: It seems safe to assume that the symptoms of pallor and general weakness that originally took this patient to his physician were due to anemia, and that the anemia was in turn due to blood loss from some lesion of the gastrointestinal tract. However, there is very little additional positive evidence to assist us in determining the type and exact location of the disease. It is known only that he had for a time, midway in the course of his illness, mild right-sided abdominal pain coming on two or three hours after meals and somewhat relieved by defecation. To this is added the information that serial films with the use of the Miller-Abbott technic about a year before the operation showed a questionable polyp-like lesion near the cecum, that is, I presume, in the lower ileum. The patient apparently had no sudden episodes of weakness or faintness followed by the passage of tarry stools. There was evidently no real intestinal colic, no diarrhea or constipation, and no epigastric pain, nausea, vomiting, heartburn or gas. When the blood count and hemoglobin were restored, his general health was apparently excellent. Physical examination revealed no mass or enlarged spleen or other sign to clarify the diagnosis.

Many gastrointestinal lesions may give rise to hemorrhage of considerable magnitude. In the upper portion of the tract, it might be esophageal varices, hiatus hernia, gastric or duodenal ulcer, gastritis, cancer of the stomach, or gastric leiomyoma or leiomyosarcoma. In the small intestine, one might encounter a malignant tumor such as lymphoma or cancer or a benign tumor such as lipoma, hemangioma, adenomatous polyp or leiomyoma; or an ulcer in a Meckel's diverticulum or, rarely, a simple ulcer of the ileum or jejunum. Very rarely, regional enteritis may cause massive bleeding. In the colon, extensive hemorrhage may come from ulcerative colitis, ulcerated polyp or cancer, particularly cancer of the cecum.

Many of these possibilities can be eliminated fairly readily. Barium studies did not reveal esophageal varices; and this, with the absence of an enlarged spleen or evidence of liver disease, seems definitely to rule them out. Hiatus hernia also may safely be eliminated in view of the negative x-ray examinations. Bleeding from gastritis must remain a possibility, although the absence of gastric symptoms is against it. The negative x-ray studies, the age of the patient, and the absence of pain and other local and general symptoms seem



local, appears to be perforation of the bowel, through either extension of the disease or radiation necrosis. She apparently died a respiratory death, possibly from pneumonia secondary to intra-abdominal sepsis.

What evidence have we for radiation necrosis? Sixteen months before entry, the patient had an operation. A cystic right ovary and tube were removed, and at that time a biopsy of the cervix was done. It is unfortunate that the biopsy was not done first. The diagnosis was epidermoid carcinoma, Grade III, and two months went by before any treatment was instituted. I am concerned about just what type of treatment was given. According to the record, roentgen-ray therapy was instituted, but no mention is made whether it was supplemented by intrauterine radium, which would make quite a difference. Obviously, the disease could not have been particularly evident to the eye, because they did the biopsy and then went ahead with a laparotomy to remove the tube and ovary. I think that one is justified in assuming that the carcinoma arose in the endocervical canal, and one may guess that by the time the patient reached the second hospital there was extension of the disease into the broad ligament, because of the slight hydronephrosis. As one continues, one finds that under treatment the hydronephrosis cleared. It may have been that the hydronephrosis was on an inflammatory basis, with sepsis giving rise to inflammatory nodes causing obstruction of the ureter, or disease may have been present that responded to radiation, thereby relieving the obstruction.

DR. TRACY B. MALLORY: The only additional information I can give you is that the patient was treated at the Pondville Hospital.

DR. PARSONS: That is very unfortunate, since I might have been responsible. However, I can now assume that the patient also had radium implantation because we believe at Pondville that roentgen-ray therapy alone, although it causes marked regression of the tumor, does not result in cure. One can get a perfectly extraordinary amount of regression of the tumor, and yet there will always be disease in the uterus unless the external radiation is supplemented by intrauterine radiation. Moreover, one should note that an operation was performed two months before the x-ray therapy. In other words, it is possible, particularly after the removal of the right tube and ovary, that the bowel became adherent at the site of the previous operation, and that as they cross-fired the radiation from one portal after another they continually hit the mesentery of a

single loop of small bowel or perhaps the sigmoid, resulting in radiation reaction to the bowel. Such a result often appears six months to years later, and is consequently a definite possibility.

Another interesting feature is that the patient was running a low-grade temperature, 99.5°F., for some time. There is no history of any previous bouts suggesting small-bowel obstruction. The obstruction is obviously not complete because on x-ray study of the abdomen no dilated bowel was apparent. Then, as a further suggestion along the line of radiation necrosis in the terminal stage, she passed 250 cc. of bright blood by rectum. Against the diagnosis of radiation necrosis and perforation is the fact that the usual picture of radiation reaction in either the small or the large bowel is one of marked thickening of the bowel wall. Whether perforation occurs in such lesions, I am not entirely sure. I have had one case of reaction in the sigmoid from radium alone in which the small bowel became adherent, resulting in perforation of the small bowel and localized peritonitis, the small bowel being involved through contiguity.

The other suggestion—that this might conceivably be due to uncontrolled cancer—is discarded if we believe in the form of treatment given at Pondville, where I treat such patients, but it is still possible that we had not controlled the disease. This was a rapidly growing, Grade III lesion. The upper part of the vagina was obliterated, and it was therefore almost impossible to tell whether disease was still present. Rectal examination did not reveal a mass and no blood was noted, but the record does not say anything about the degree of the fixation of the pelvis.

In conclusion, I believe that this patient had radiation reaction of the bowel and general peritonitis; the physical signs of a dilated stomach, probably due to ileus were present. On the other hand, she did not have dilated loops of small bowel. Although she had distant peristalsis, there was no spasm and no tenderness of the abdomen, which worries me a little bit. It is possible that she had an embolus and that the radiation reaction that I believe was present still did not have anything to do with her death. She had moderately low-grade fever, 99.5°F., and general malaise. She had been hospitalized for a previous operation, and it is possible that at that time she had a deep phlebitis and that death may have occurred from pulmonary embolus, the radiation reaction being an entirely secondary and incidental finding. I am inclined to go out on a limb, however, and say that this patient died of peritonitis and pneumonia, and that the peritonitis was due

to perforation of the bowel secondary to perforated radiation necrosis of the bowel or possibly perforation secondary to uncontrolled disease.

DR ALLEN G BRAILEY: Were x-ray films taken of the lungs?

DR MALLORY: I do not believe so.

#### CLINICAL DIAGNOSIS

Pelvic peritonitis.

#### DR. PARSONS'S DIAGNOSES

Peritonitis, secondary to perforated bowel, from radiation necrosis

Pneumonia

#### ANATOMICAL DIAGNOSES

Metastatic carcinoma, from carcinoma of the cervix.

Thrombosis of mesenteric, splenic and portal veins

Infarction of the small intestine, acute

Peritonitis, hemorrhagic, early.

Occlusion of cervical canal of uterus.

Pyometrium.

Cholecystitis, with cholelithiasis.

Operative wound, healed, right salpingo-oophorectomy.

#### PATHOLOGICAL DISCUSSION

DR MALLORY: The surgeons who took care of this patient on the wards were no more anxious to commit themselves than Dr. Parsons. They

thought that she probably had a pelvic peritonitis, but they did not specify the cause thereof.

At post mortem examination, it was found that nine tenths of the small bowel was completely necrotic, swollen, thickened and dark red and contained blood in its lumen. There was also free blood in the peritoneal cavity. The mesenteric, portal and splenic veins were completely thrombosed. The arterial supply of the small bowel was still apparently functioning. It was also found that the radium treatment had dealt satisfactorily with the local tumor. The cervical canal was completely obliterated. There was a pyometrium, but we could find no carcinoma in the uterus or immediate adnexa. However, the retroperitoneal lymph nodes were filled with metastases, one node was large enough so that it seemed to press on the mesenteric vein, and we thought that that, perhaps, was the immediate reason for the mesenteric thrombosis. However, it was merely a guess. I have not seen generalized venous mesenteric thrombosis result from radiation therapy and do not remember to have heard of it. I therefore doubt if the radiation was responsible. Certainly, there was none of the marked fibrous thickening of the bowel usually seen in radiation necrosis.

The lungs showed chiefly atelectasis and edema, although there was very slight beginning bronchopneumonia. There were a few other incidentals of not very great importance, the most striking one being a gall bladder containing a score of gallstones.

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established in 1828

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND  
PUBLISHED UNDER THE JURISDICTION OF THE COMMITTEE  
ON PUBLICATIONS

Official Organ of  
THE MASSACHUSETTS MEDICAL SOCIETY  
and  
THE NEW HAMPSHIRE MEDICAL SOCIETY

## EDITORIAL BOARD

Joseph Garland, M.D.	Stephen Rushmore, M.D.
William B. Breed, M.D.	Henry R. Viets, M.D.
George R. Minot, M.D.	Robert M. Green, M.D.
Frank H. Lahey, M.D.	Charles C. Lund, M.D.
Shields Warren, M.D.	John F. Fulton, M.D.
George L. Tobey, Jr., M.D.	A. Warren Stearns, M.D.
C. Guy Lane, M.D.	Dwight O'Hara, M.D.
William A. Rogers, M.D.	Chester S. Keefer, M.D.

## ASSOCIATE EDITORS

Thomas H. Lanman, M.D.	Donald Munro, M.D.
Henry Jackson, Jr., M.D.	

Walter P. Bowers, M.D., EDITOR EMERITUS  
Robert N. Nye, M.D., MANAGING EDITOR  
Clara D. Davies, ASSISTANT EDITOR

SUBSCRIPTION TERMS \$6.00 per year in advance, postage paid, for the United States (medical students, \$3.50 per year), Canada, \$7.04 per year, Boston funds, \$8.52 per year for all foreign countries belonging to the Postal Union

MATERIAL for early publication should be received not later than noon on Friday

THE JOURNAL does not hold itself responsible for statements made by any contributor

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston, Massachusetts

## A CHALLENGE TO FEDERAL, STATE AND LOCAL HEALTH DEPARTMENTS

WAR activities have produced some new health problems, but what is more important, they have served to focus attention on some old problems and to render certain ones more acute. The health of the soldier is vital, but so is the health of civilians, both because of the chance that soldiers may become infected from them, and because the urgency of producing articles of war demands that all workers be able to continue their tasks without absence due to illness.

Most problems that are arising are due to a shifting of populations. Not only are military forces being concentrated at given places, but to

care for their needs, concentrations of civil populations are built up in the areas immediately surrounding such military establishments. War industries are also causing concentrations of civilian populations at points where the plants are located. Frequently, because of such concentrations, water supplies become inadequate and have to be supplemented from sources less reliable than the regular ones. Facilities for community sanitation become overtaxed and create situations that may allow the spread of communicable diseases. Conditions are most acute in the boom-town areas, where thousands of people flock into communities that formerly consisted of only a few hundreds of inhabitants.

These conditions are a challenge to federal, state and local health authorities. If the health of the nation is to be safeguarded in these strenuous times, efforts must be redoubled, and vigilance should be kept at a high level to guard against unsatisfactory conditions. Steps have already been taken to meet the challenge. The personnel of the United States Public Health Service has been considerably expanded; liaison officers have been assigned to all the military areas to aid in arranging for the co-operation of medical officers of the United States Army and Navy and the civilian health authorities. Federal funds have been made available to expand the staff of many state health departments, and other sums have been allocated to assist in providing water supplies, sewerage and housing developments in the areas most acutely affected. Local health authorities have accepted their responsibilities and have increased their activities to guard the health of the newcomers to their communities.

The Honorable Paul V. McNutt, administrator of the Federal Security Agency, in an address before the annual conference of state and territorial health officers in Washington, D. C., last spring, called attention to three of the most critical problems of the immediate future: industrial hygiene, medical and hospital care, and nutrition. These three problems have already received the serious consideration of health authorities, and definite plans are being formulated to find the best solutions for them.

New England is fortunate in that there are few areas in which the problems are so acute as they are in other parts of the country. Water-supply systems and facilities for community sanitation have usually been provided to care for considerable increases in population, so that, up to the present time, few have been overtaxed. This should not, however, result in a false attitude of security, and every available means to guarantee the continued health of military and civilian populations should be utilized by federal, state and local health departments.

---

### KAREL FREDERIK WENCKEBACH

In the thunder and rumble of war, few people abroad and on this side of the Atlantic took notice that a heart had stood still that had been beating a lifetime for the benefit of countless other hearts. It was that of a man without whose work cardiology would not be what it is today.

Karel Frederik Wenckebach was born in 1864 in The Hague. After his graduation and a short interlude in anatomic and embryologic research he was compelled, for financial reasons, to give up his theoretical dreams and to go into rural general practice. His keen interest in scientific problems was not stifled; however. With a primitive sphygmographic apparatus, he made a series of fundamental discoveries, giving the first description and analysis of extrasystoles in the human heart and of disturbances in auriculoventricular conduction (*periodically dropped beats*).

His reputation became so outstanding that he was invited in 1901 to accept the vacant chair of clinical medicine at the ancient University of Groningen, Holland, an unprecedented honor for a young country doctor. A call to the University of Strasbourg followed in 1911, and in 1914 Wenckebach was appointed chief of the First Medical Clinic of the University of Vienna, which at this time was still one of the leading medical schools of the world.

Like most pioneers, Wenckebach had to overcome the opposition of more conservative groups of teachers, but with the appearance of his standard work on the cardiac arrhythmias in 1903, his

position among the prominent scientists of his time became firmly established. In this classic book, he stressed the fact that arrhythmias do not always indicate an organic lesion of the myocardium but that, on the other hand, they are apt to lead to cardiac failure. In the second edition, published in 1914, quinine was recommended as a useful drug in cardiac disorders for the first time since 1749, when Senac, a physician to the Court of Paris, prescribed it for obstinate palpitation; the action of the drug was rediscovered by a patient of Wenckebach, and its value in cardiac arrhythmias was proved by him. Although in this edition only one single electrocardiographic curve was reproduced, the epoch of both sphygmographic and electrocardiographic arrhythmia research was brought to a successful conclusion in Wenckebach and Winterberg's monumental monograph, which appeared in 1927 and is still unsurpassed.

Wenckebach's work on the beriberi heart, carried out in the Dutch East Indies in 1929-1930, was the forerunner of the present conceptions regarding vitamin deficiencies in the circulatory system. His widely appreciated book on cardiac failure gave further proof of his keen clinical observation.

All in all, Wenckebach was one of the founders of modern cardiology. Many of his basic discoveries became so soon accepted as commonplace facts that their origin fell into undeserved oblivion. However, some of these are even today connected with the name of their discoverer: the "Wenckebach periods," the "Wenckebach bundle" and the "Wenckebach sign" of adhesive pericarditis.

The First Medical Clinic of Vienna was for years the goal of numerous European and American graduate students, in the fields of both cardiology and general internal medicine. Important diagnostic and therapeutic achievements originated under Wenckebach's guidance, such as the discovery by Saxl of the powerful diuretic effect of certain soluble mercury compounds, which greatly facilitates the treatment of congestive heart failure.

Wenckebach was by no means a dull, dry professional man, absorbed in scientific problems. His active interests roamed far and wide in the realm of the arts and literature, and his beautiful home,

with its choice paintings, sculptures and pottery, was an international center of intellectual and artistic life. His unusually charming and lovable personality, as well as the enormous dimensions of his private practice, brought him into close contact with a large number of Europe's most interesting people. A perfect gentleman, with a liberal, open mind, he knew how to enjoy life in a noble, refined way and also how to make it enjoyable for others.

Wenckebach's intimate friendship with outstanding British investigators, such as Mackenzie and Keith, enabled him to visit London after World War I, while the blockade was still in effect, to secure food transports for the starving Austrians and to save the famous Gobelin tapestries in Vienna from being sold for bread. After having completed a lecture tour through the United States in 1923, he often referred enthusiastically to the idealism and unbiased critical spirit of American scientific workers, which impressed him even more than the amazing technical facilities available in this country, and in his last letters to former pupils he expressed a hopeful belief in the present and future leadership of American medical research.

MEDICAL EPONYM

MORTON'S TOE

Thomas G. Morton (1835-1907), surgeon to the Philadelphia Orthopedic Hospital, described this condition in a paper, entitled "A Peculiar and Painful Affection of the Fourth Metatarso-Phalangeal Articulation," published in the *American Journal of the Medical Sciences* (71: N. S.: 37-45, 1876). He reported 15 cases, 13 of which were in women. All the patients complained of severe pain localized in the fourth metatarsophalangeal articulation. It was generally relieved by removal of the shoe. Some patients told of having to stop in the street for this purpose. Morton advised operation for the relief of chronic cases. The origin of the condition is described as follows:

To the peculiar position which the fourth metatarso-phalangeal articulation bears to that of the fifth, the great mobility of the fifth metatarsal, which by lateral pressure is brought into contact with the fourth, and lastly, the proximity of the digital branches of the external plantar nerve, which are under certain circum-

stances liable to be bruised by or pinched between the fourth and fifth metatarsals, may be ascribed the neuralgia in this region.

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

COMMITTEE ON MATERNAL WELFARE

CAUSES OF MATERNAL DEATH IN  
MASSACHUSETTS DURING 1940 (concluded)

Table 1 gives the final and correct classification for maternal deaths occurring in Massachusetts during 1940. Since the publication of the original table in the January 8 issue of the *Journal*, 2 cases have been added; but because the 2 deaths in women who were not pregnant have been dropped, the total (219 deaths) is the same. The most striking conclusions to be drawn from this study are covered by the following paragraphs.

There were 58 autopsies. This number is somewhat less than that for the cases in 1939. The value of autopsy cannot be emphasized too strongly. In certain cases, in no other way may an exact diagnosis be arrived at. It would be very

TABLE 1. Causes of Maternal Death.

CAUSE	NO. OF DEATHS
Sepsis	50
Medical diseases	42
Embolism	29
Hemorrhage	27
Eclampsia	24
Surgical conditions, including shock	15
Transfusion reaction	8
Rupture of uterus	8
Anesthesia	8
Ectopic pregnancy	6
Pernicious vomiting	2
Total	219

helpful, as well as informative, if the medical examiners used their authority in demanding autopsies on cases of maternal death that came under their jurisdiction. Red tape and sentiment are the reasons why more permissions for autopsies in this group are not obtained. Several of these cases had only a clinical diagnosis, which would undoubtedly have been proved false could an anatomical diagnosis have been made.

Reference has previously been made to the diminution in the number of deaths due to sepsis, and to the large percentage of deaths due to criminal abortion. Chemotherapy undoubtedly has played a large part in this fortunate decline. Undoubtedly, also, improved obstetric operating and an absence of bungling operating have been contributory.

Among the medical deaths, those definitely attributed to pneumonia emphasize the value of the

treatment of the common cold and the necessity for early diagnosis of pneumonia if chemotherapy is to be of any value. Heart disease has been proved to be a serious complication of pregnancy, as the number of patients who died undelivered bears evidence.

Several of the cases allocated to embolism may have been preventable. Undoubtedly, some of these cases had a low-grade phlebitis that was not recognized, and might have been treated successfully by surgery. Such methods of treatment, however, are new, and the patient must be treated only by surgeons particularly trained in this field.

The deaths attributed to hemorrhage are so closely allied with transfusion, or the lack of transfusion, that the two may be discussed together. It was surprising how many of the patients who died of frank blood loss were not given the benefit of the injection of whole blood. Blood banks are not yet established in some of the large municipal hospitals, so that one cannot criticize the lack of them in small, local institutions. But whole plasma is on the market, and although it does not always take the place of whole blood, it certainly tides the patient over in many cases that would otherwise result fatally. The 8 patients who died of transfusion reaction, of course, represent a very small percentage of the cases in which transfusion was used. And yet one cannot help believing that in some institutions the technic of matching and cross-matching has not been properly developed.

Under the cases allocated to eclampsia, some bring out the fact that many women in Massachusetts still have no prenatal care. Practically none of these women should have died. In only 1 case did poor obstetric operating play a major part in the fatality, but in many, unintelligent procrastination on the part of the medical attendant was the real reason for the death.

There is little to be said of the cases allocated to surgical conditions, which include mesenteric thrombosis, appendicitis, intestinal obstruction and surgical shock. Once more, it should be emphasized that intestinal obstruction does not lend itself to delay.

Several of the patients with rupture of the uterus died because of poor obstetrics, particularly those who died undelivered. Such fatalities can in no way be condoned. And those patients with rupture of the uterus, at the beginning of labor, on whom cesarean sections had previously been done, emphasize that such ruptures do occur, and that if one chooses to allow these patients to go through labor, they should be hospitalized at the very first sign of labor and watched very carefully, with the understanding that a laparotomy may be necessary.

The 8 deaths due to anesthesia are far too many; of course, all were preventable.

Under ectopic pregnancy, the unusual case of abdominal pregnancy has previously been mentioned. Any abdominal pregnancy is a serious condition. In this case, the diagnosis was entirely missed. The 5 patients with tubal pregnancies who died of massive hemorrhage, without operation, show how serious the condition may be; there must have been previous bleeding that went unrecognized, either because of the patient's ignorance or because of the ultraconservatism of the physician.

That pernicious vomiting may still cause death means only that patients are ignorant or negligent in reporting to their physician, or that the physician is ignorant or unintelligent in his treatment of this complication.

The committee once again expresses appreciation for the time and energy spent by the physicians who investigated these deaths in different parts of the State. It also thanks the physicians interviewed for their willingness, almost without exception, to co-operate with the investigators. The deaths for one more year, 1941, remain to be classified, and the investigation is now under way. The national emergency will make this study more complicated, because some of the physicians whose cases resulted fatally will have been called to war. This is appreciated, but under these circumstances, hospital authorities are requested to instruct their record departments to be most lenient in allowing investigators, who sometimes have come many miles, to look up facts about these cases. Unfortunately, there has been hesitancy to grant this privilege in the past.

#### "TUBERCULOSIS IN CHILDREN"\*

It might be interesting to those who are listening if I simply stated a few of the questions most frequently asked by the parents and other relatives of patients at the Children's Hospital when the question of tuberculosis is raised. Some points recur so commonly under those circumstances, and we have had to explain some things so often, that I am sure many people lack information about them.

The first question asked is, Do children or babies really have tuberculosis? The answer is obviously that they do, and also that they have it oftener than the public realizes. The way tuberculosis shows itself (or fails to show itself) differs in child patients from the way it acts in adults, but children and even babies as young as a few weeks of age may and indeed do have the disease.

Another question often asked is, Do they inherit it? The question may be asked in another way, when the

\*A "Green Lights to Health" broadcast given through Station WAAB by Dr. Clement Smith on November 29, 1941, and sponsored by the Public Education Committee of the Massachusetts Medical Society and the Massachusetts Department of Public Health.

parents of a tuberculous child say: "None of my relatives have tuberculosis; I don't see how my child could have gotten it." To answer the last statement first, it may be pointed out that one of the very important things about this disease in general is that many tuberculous people have so few symptoms or such indefinite symptoms that they do not suspect that they are ill. But beyond that point, it should be said that the disease is not inherited by children. Physicians often say, and probably with reason, that although tuberculosis itself is not passed on from generation to generation, some families seem to inherit a susceptibility to it, or seem by virtue of their inherited constitution to be likelier to develop it, but the actual condition of being born with the germ of tuberculosis in the body, although even that occurs very rarely, is, generally speaking, not the way babies get tuberculosis. Tuberculosis comes from tuberculosis, not by inheritance but by catching the germs of the disease just in the same way that whooping cough is caught from someone who has whooping cough. It may take a good deal of contact with a tuberculous person to infect a child with the disease, but not necessarily, since perfectly definite cases have been traced to only one meeting between an uninfected child and a diseased adult. Undoubtedly, numerous cases of infection occur quite by chance in crowded places, — when children are taken into streetcars or stores, or places of amusement, — since the more people a child is in contact with, the more probable it is that some of them may be harboring the germs that may infect the child. But by all odds, the commonest single place where children and babies acquire tuberculosis is in the very place where they ought to be safest, that is, in their own homes, and this is a strange thing when one thinks that traditionally the home constitutes the barrier that parents build as the one place of refuge for their children against the dangers of the world. Of course, the source of the infection at home is usually an older person, who either has the disease and refuses to do anything about it or, more commonly, has it and is not aware that he has it. One leading professor of children's diseases has made the very true statement, "There are two ways to find that a man has tuberculosis — one is to find the germ in his sputum, the other is to find the disease in his baby." This is equally true, of course, of a mother.

A fourth question is asked in this way: "I don't see how the child can have tuberculosis, Doctor, because he has never been sick. In fact, he is one of the healthiest-looking children in his school. He is not thin, he's full of energy, and he doesn't cough." That question brings up the whole peculiarity of tuberculosis in general, and particularly of the disease in children and babies. As you know, it may smolder in adults like a concealed fire somewhere under the surface and without any signs of itself until gradually it progresses to a stage where symptoms occur. At first, these are very indefinite ones of tiredness, loss of weight and so forth. In babies and children, this peculiar lurking quality of tuberculosis is even more evident, so that we find it to be present, and quite often present to a rather widespread degree, in children who are fat and happy, and have no cough or other symptoms. Therefore, a very important thing about handling the tuberculosis problem in childhood and infancy is that we must look for the disease before it has gone far enough to show the signs that the public usually associates with it. One tragic thing is that often in young babies the first outward symptoms that a mother or father observes may be the indications that the disease has gone beyond the

point where there is any hope of bringing about a recovery.

A fifth question, which follows from this former one is, of course, How can the disease be found before any symptoms appear? Fortunately, there are several very good procedures for doing this, none of which take very much time or trouble. Of course, one thing of prime importance is to apply these procedures, if not to all children in the population, at least to children whose parents or relatives are known to have the disease and who might thus have been exposed to it.

The means of searching are first of all the simple and highly reliable tuberculin test, which as performed at present requires a nearly painless needle prick, although a method is now being developed that avoids even the needle prick by simply applying the testing substance against the skin under a strip of adhesive tape for a few days. No particular danger or discomfort is associated with either of these tests, even if a reaction develops. If properly performed and interpreted, the test should pick out practically all the children into whose bodies the germs of tuberculosis have entered. The ones who show that this has happened can be given an x-ray examination of the chest, to reveal whether the infection is in a severe state, or whether it is so mild as simply to need repeated examinations during the course of childhood.

And, since in considerable part the danger is determined by the x-ray findings, this naturally leads to the sixth and very crucial question on the part of the parents and relatives, "How dangerous is tuberculosis in a baby or child?" This question must be answered in a particular and not a general manner, because so much depends on the age of the child and on how far the disease has progressed before it has been discovered. In general, it may be said that all babies up to the age of two or three years do not do so well with the disease as older children do, so that there exists a high point of greatest danger during the second year of life. After this, the danger diminishes a good deal, so that between the ages of seven and twelve children seem to have a remarkable resistance, at least to tuberculosis of the lungs. After that, when children, particularly girls, get into the teens, the resistance is lessened and the outlook for a tuberculous child of fourteen or fifteen may become as serious as that for a tuberculous infant. But even in infants who have not much resistance if we can discover the infection early and get the child under care at that time, certainly at least 90 per cent of patients will do well. On the other hand, if the disease is not brought to attention until symptoms develop, the figure may be nearer 50 per cent, with a much greater number of children who do not survive — a striking example of the value of finding the infection early in those babies and children who acquire it.

How long does it take to get better? That is not an easy question to answer, but we have noticed at the hospital that, if a child is doing well twelve months after we first find the disease, we can expect him to do quite well thereafter; therefore, we can tell parents (even the parents of small infants in a dangerous age) that when we have known their child for a year we can give them a much brighter outlook. But we can never drop an infected child from some sort of care then or even thereafter. We do not need to keep the child an invalid, but we consider it proper for all these children to be examined once a year through childhood and adolescence, and preferably until they are at least twenty-five years old for the sort of insurance that an annual examination gives. At such annual examinations, during adolescence, it may

be wise to take an x ray film for checkup purposes. In the safer age period of midchildhood, repeated annual x ray studies are probably not required. Of course, these children do not need to be invalids all this time, and almost all, after the critical first year has passed (and some times before that), can be allowed to lead perfectly normal lives.

What is the best treatment for babies and children with the disease? Unfortunately, we have no medicine that kills the tuberculosis germs at present, although we live in hope. Some children, particularly those in whom the lungs are diseased in adolescence, may need special air injection treatment to rest the involved lung. In the large majority of patients, all we can do is to believe that bringing about the best possible state of general health for the child will offer him the greatest chance for complete permanent recovery. This may mean cure in a sanatorium; it may mean rest at home, it may mean special medicine and diet to build up the child or it may mean that the child is already in such good household surroundings that we need do little further except to supervise the parents' care. But that brings up another important thing—which is that the child should no longer remain in contact with diseased adults who may be passing on the infection to him, so that one very important thing that we can do just as soon as we find an infected child is to make sure that no one in the household is (either knowingly or unknowingly) diseased and thus acting as a source of germs that may be passed further to the patient. This requires co-operation on the part of the parents and a certain amount of work in arranging for examinations, but in the long run it is helpful not only to the child but to the parents, and of course to any other children in the family.

In conclusion, it is appropriate to bring up the question, How are these things done? In Massachusetts, they are done in part by an expert body of state and city workers, who, fortunately, have a very well staffed and well-equipped group of hospitals and sanatoriums to which patients may be sent. But by no means does all the budget for this kind of work come from the state and municipal funds, in fact, a large part of it comes from the Massachusetts Tuberculosis Association and is supported by the Christmas Seal sale. In the numerous jobs that have to be done to straighten out the family situation and to heal and to protect the child with tuberculous infection, we are constantly helped by things that the Christmas Seal sale has made possible. If it becomes necessary to send the child to a more healthful environment than he can have at home, we may find care for him in such a place as the Prendergast Preventorium, which is actually supported by the annual Seal sale. If it is necessary to help his convalescing father to find work, the Sheltered Workshop, which is also supported in this way, may be of assistance. There are many other important ways in which the money that you pay for Christmas seals reaches the situation in a way that makes you yourself an effective agent in meeting problems that are commoner than you may realize.

## DEATHS

**DALTON**—CHARLES H. DALTON, M.D., of Somerville, died February 12. He was in his sixty-sixth year. Born in Charlottetown, Prince Edward Island, Dr. Dalton received his degree from McGill University Faculty of Medicine in 1901. He was on the staff of the Somerville Hospital, and was a fellow of the Massachusetts Medical Society and the American Medical Association. He is survived by his widow and five sisters.

**WAKEFIELD**—ARTHUR PAUL WAKEFIELD, M.D. of Belmont, died February 6, in his sixty-fourth year. Born in North Bloomfield, Ohio, he graduated from Hiram College in 1900 and received his M.D. degree from Rush Medical College in 1904. After a brief period of private practice, he went to China as a medical missionary and remained there for twenty-two years. He was in charge of a hospital in Luchowfu from 1912 to 1916 and then became director of student health at Boone University at Wuchang. This position he held until the Chinese revolution of 1927 made it necessary for him to leave the country. The Chinese National Red Cross decorated him for flood relief on the Yangtze and reconstruction work at Wuhu. On his return to America, he supervised the school clinics conducted by the Massachusetts Department of Public Health for five years, and then became superintendent of the Central Maine Sanatorium at Fairfield. He returned to the Massachusetts Department of Public Health in 1937 and was given the task of organizing and directing the Clinics for Crippled Children. Under his guidance, these clinics have been very successful in bringing aid to hundreds of handicapped children. His crusading spirit, kindness and persistency in the face of obstacles made him exceptionally well qualified for this type of work.

His widow, a son and two daughters survive him.

## WAR ACTIVITIES

### CIVILIAN DEFENSE

#### RELATION OF RED CROSS CHAPTERS TO DEFENSE COUNCILS

A joint statement of policy governing the relation of Red Cross chapters to state and local defense councils, as developed by the Office of Civilian Defense, Office of Defense Health and Welfare Services, and the American Red Cross, was issued December 28 and published in *Victory*, the official weekly bulletin of the agencies in the Office for Emergency Management, as follows:

I. The Red Cross through its chairman is a member of the Civilian Protection Board has made available all of its services as needed by the United States Office of Civilian Defense and state and local defense councils. As illustrative of its national services, attention is called to the programs involving blood plasma, medical technologists and nursing enrollment. The Office of Civilian Defense and the American Red Cross are agreed that defense councils and Red Cross chapters should develop local plans of co-operation in their civilian-defense activities.

II. Recognizing the basic responsibility of government, it is the duty of every Red Cross chapter and branch to aid in the most efficient marshalling of the community's resources. It is agreed that duplication should be avoided in these services and training courses required in civilian defense activities and that the long-established nationwide program of the Red Cross should be utilized to the fullest extent.

III. Services required in civilian-defense activities will be made available by chapters to defense councils in accordance with the policies herein stated. Chapters will co-operate to the fullest extent and, during the period of emergency, will operate subject to the authority of the defense councils or appropriate governmental officials. The Red Cross at all times will maintain administrative and financial control of its immediate operations.

IV. Chapters should expand Red Cross services and training courses within the scope of their responsibility.



so that they may be prepared to give such services as are needed in the local programs of defense councils.

V. In the specific application of the above general policies, it is agreed that the areas of Red Cross responsibility shall be:

1. Red Cross chapters will be prepared to function, in the following fields of activity in full co-operation with all public and private agencies:

*a.* Disaster relief—training and service—food, shelter, clothing and other necessities of life in the event of disaster, whether occasioned by belligerent action or other cause.

*b.* First aid—training.

*c.* Nurse's aides—training and service.

*d.* Red Cross home nursing—training.

2. Red Cross chapters will assist defense councils in the following fields on the basis of mutual specific agreements as to lines of responsibility:

*a.* Disaster relief—service—will assist local defense councils in rescue work and emergency medical care.

*b.* Nutrition aides—training and service.

3. Red Cross chapters will make available to defense councils as needed the services of the following volunteer special service units, which shall at all times maintain the Red Cross unit organization (see III above):

*a.* Motor corps—service.

*b.* Production corps—service.

*c.* Staff assistance corps.

*d.* Canteen corps and canteen aides—service.

*e.* Hospital and recreation corps—civilian hospitals—service.

4. Red Cross chapters in their services to the armed forces are fully responsible for the following activities:

*a.* Information and claims—service.

*b.* Communications and reports.

*c.* Consultation on personal and family problems.

5. The functions of Red Cross chapters adjacent to Army posts and Naval stations include the following:

*a.* Hospital recreation corps—training and service—in military hospitals.

*b.* Motor corps—training and service—service originating on military reservations.

*c.* Production corps and staff assistance corps—activities on military reservations.

*d.* Participation in Red Cross camp and hospital-service councils.

6. Junior Red Cross:

*a.* The participation of boys and girls in elementary and secondary schools in Red Cross services through Junior Red Cross programs should be maintained in the same relation to local defense councils and to the armed forces as is established in this statement with respect to its parent organization. Junior Red Cross activities will be channeled through the local Red Cross chapter.

*b.* Red Cross chapters will make available to defense councils as needed those activities of the Junior Red Cross which contribute to the health, welfare and unity of schools and communities.

## NEW HAMPSHIRE MEDICAL SOCIETY

### DEATHS

DAUDELIN—ALFRED DAUDELIN, M.D., of Nashua, died September 21. He was in his sixty-fourth year.

Born in Nashua on June 6, 1878, Dr. Daudelin received his degree from Baltimore Medical College in 1908. After practicing in Somersworth, he returned to Nashua, where he held memberships in the county medical association, the New Hampshire Medical Society and the American Medical Association. He served on the Nashua Board of Health for several years, and was a former city and county physician.

His widow, Mrs. Eugenie Daudelin, and a sister, Miss Phoebe Daudelin, survive him.

DEMING—ROBERT M. DEMING, M.D., of Glenduff, died January 28. He was in his forty-ninth year.

Born in Elizabethtown, New York, Dr. Deming attended Colgate University and received his M.D. degree from University of Vermont College of Medicine in 1916. He served for two years with the British Medical Corps in World War I. He was superintendent and medical director of the New Hampshire Tuberculosis Sanitarium, and was a member of the National Tuberculosis Association and a fellow of the New Hampshire Medical Society and the American Medical Association.

He is survived by his widow, Mrs. Lolita Smith Deming, and his mother, Mrs. Mabel S. Deming, of Ballston Spa, New York.

SANBORN—BENJAMIN E. SANBORN, M.D., of Manchester, died October 3. He was in his fifty-seventh year.

Born in Deerfield, Massachusetts, in 1885, the son of Benjamin E. and Alice (Johnson) Sanborn, Dr. Sanborn received his degree from Dartmouth Medical School in 1911. He spent the next three years as an intern at the Massachusetts State Hospital and at the Rhode Island Hospital, and established his medical practice in 1914. He was a member of the New Hampshire Medical Society and the American Medical Association.

He is survived by his widow, Mrs. Shuah Hobbs Sanborn.

## MISCELLANY

### TEWKSBURY STATE HOSPITAL AND INFIRMARY

Dr. Lawrence K. Kelley has recently resigned as superintendent of the Tewksbury State Hospital and Infirmary; he plans to re-enter private practice. To date, the vacancy has not been filled by the trustees of the institution.

# RESUME OF COMMUNICABLE DISEASES IN MASSACHUSETTS FOR DECEMBER, 1941

DISEASES	DECEMBER 1941	DECEMBER 1940	FIVE YEAR AVERAGE*
Anterior poliomyelitis	7	0	1
Chicken pox	1603	1680	14 0
Diphtheria	19	9	18
Dog bite	577	591	559
Dysentery bacillary	16	3	13
German measles	68	48	53
Gonorrhea	273	294	423
Measles	678	1165	1101
Meningitis meningococcal	12	7	6
Meningitis other forms	6	—	—
Mumps	1460	597	475
Paratyphoid infections	4	1	3
Pneumonia lobar	708	407	437
Scarlet fever	1171	642	648
Syphilis	335	376	412
Tuberculosis pulmonary	228	314	264
Tuberculosis other forms	28	28	29
Typhoid fever	8	6	8
Undulant fever	3	5	5
Whooping cough	828	1161	983

\*Based on figures for preceding five years

## GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Anterior poliomyelitis was reported from Easthampton, 4, Fort Devens, 1, Hardwick, 1, Somerville, 1, total, 7

Anthrax was reported from Lynn, 1, total, 1

Diphtheria was reported from Boston 2, Everett, 1, Fall River, 8, Lowell, 1, Norfolk, 1, Palmer, 1, Somerville, 1, Springfield, 1, Stoughton, 1, Taunton, 1, Webster, 1, total, 19

Dysentery, bacillary, was reported from Boston, 1, Brockton, 1, Easthampton, 3, Fall River, 2, Northampton, 1, Waltham, 8, total, 16

Encephalitis, infectious, was reported from Haverhill, 1, total, 1

Meningitis, meningococcal, was reported from Boston, 2, Brockton, 1, Fitchburg, 1, Framingham, 1, Gloucester, 1, Mendon, 1, Milton, 1, New Bedford, 1, Norwood, 1, Waltham, 1, Worcester, 1, total, 12

Meningitis, other forms, was reported from Gloucester, 2, Haverhill, 1, Norwell, 1, Salem, 1, Waltham, 1, total, 6

Paratyphoid infections were reported from Marblehead 1, Medford, 1, Salem, 1, Westwood, 1, total, 4

Pellagra was reported from Boston, 1, Quincy, 1, total, 2

Septic sore throat was reported from Boston, 6, Boxford, 1, Cambridge, 1, Everett, 1, Fall River, 3, Greenfield, 1, Malden, 1, Plymouth, 1, West Springfield, 1, total, 16

Tetanus was reported from Wakefield, 1, Woburn, 1, total, 2

Trachoma was reported from Worcester, 1, total, 1

Trichinosis was reported from Attleboro, 5, Camp Edwards, 3, Chelsea, 2, Everett, 1, Wakefield, 1, total, 12

Tularemia was reported from Lawrence, 1, total, 1

Typhoid fever was reported from Boston, 3, Chelsea, 1, Danvers, 1, Newton, 1, Stoughton, 1, Wellesley, 1, total, 8

Undulant fever was reported from Boston, 1, Northbridge, 1, Webster, 1, total, 3

Mumps continued to show record high incidence for the sixth consecutive month

Bacillary dysentery, chicken pox, diphtheria, dog bite, German measles, meningococcal meningitis, paratyphoid infections and scarlet fever were reported above the five year averages

Typhoid fever was reported at a figure equal to that for the five year average.

Measles, pulmonary tuberculosis, tuberculosis, other forms, undulant fever and whooping cough were reported below the five year averages

Lobar pneumonia showed record low incidence

The focus of animal rabies which has been noted in the northeastern section of the State is still active in Middlesex County, cases having been reported from Burlington, Wilmington and Woburn

## REPORTS OF MEETINGS

### SUFFOLK DISTRICT MEDICAL SOCIETY

At the regular fall meeting of the Suffolk District Medical Society, October 22, presided over by Dr Albert A. Hornor, Dr Harold C. Stuart discussed 'Experiences in Unoccupied France during 1940-1941'. The Rockefeller Foundation, which for sixteen years had been at tempting to develop an efficient public health service in France, withdrew at the beginning of World War II, only to return following the fall of France, it was to establish such a service that Dr Stuart, among others, was asked to go to France. He recounted the delays and in conveniences caused by the lack of co-operation by the civil authorities, although promises had been given and arrangements made many months before. But finally he and his associates were able to set up a sort of regional institute at Marseilles

Some idea of the state of affairs in Marseilles may be gleaned from a comparison with a city such as Boston, of approximately the same population. In the first place, 500,000 refugees entered the crowded city, then the confiscation of 140,000 freight cars from France (with as much cattle and produce as they held) markedly decreased the facilities for transportation of people and food, the lack of fuel further limited the amount of travel, even though some compensation resulted later from the conversion of larger trucks and buses into wood burners; even power plants were curtailed in fuel, thereby further limiting tramway travel. Two million five hundred thousand prisoners in Germany decreased the manpower to critical levels and made the task of those remaining more difficult. Recreation was so restricted that people went to drab cafes and dull theatres only to take advantage of the warmth afforded by the crowds. The existence for foreigners was particularly trying, since they could obtain no work without a citizen's certificate nor any relief from the community. The eventual result was their getting into trouble and being sent to concentration or work camps, in which the living conditions were inconceivably bad, no attempt to improve them being made.

In regard to the food situation in Marseilles, which was the particular problem of Dr Stuart, the most notable lacks were of animal proteins and fats. This was especially trying on infants and children, who were allotted one and a half pints of milk below eighteen months of age and one pint between eighteen months and five years. Nobody over five years was allowed milk at any time, and even the above schedule far from assured the children sufficient milk. Bread rations were decreased from 350 to 240 gm per day, 90 gm of almost inedible goat and horse meat was allowed about twelve times a month, 15 gm of vegetable fat a day, 1 pound of sugar a month, and 20 gm of cheese, which was considered a real delicacy, five times a month. Obtaining food was usually the most difficult task, often requiring a three hours' wait to obtain little or no food. Therefore, Dr

Stuart and his group stayed in hotels where the more placid and acclimated natives endured the delay.

For the scientific study that was carried on, the group attempted to obtain a crosssection of the population and to measure the intake of various foods. There were 100 families, in addition to 100 children (for age distribution), so studied, and appropriate blood studies were carried out. Incidentally, most of the equipment arrived from America either very late or not at all. The subjects were observed for intake in the home, and then underwent a physical examination at the clinic. Although citrus fruits were virtually unknown, and the blood ascorbic acid levels were invariably zero, no examples of true clinical scurvy were found. Vitamin A levels were also low. The protein values, on the other hand, were not appreciably lowered, and the erythrocyte and hemoglobin counts were satisfactory. The failure of iron-deficiency anemias to occur was attributable to the importation of boatloads of green vegetables from the African colonies during the winter and spring. The high phosphatase levels could be expected from the high incidence of rickets, which was not much different from that in prewar times. The results of these preliminary studies were about what might be expected in a country where a severe shortage has been felt for only a relatively short period. There were many early manifestations of deficiency syndromes, and more recent reports indicate that severer deficiencies are already appearing and promise to become commoner during the winter.

Dr. Stuart described the relief work being carried on by the Swiss and American organizations, which act in the role of medical advisers to the population. In this manner, the relief workers were able to obtain the confidence of the people, who were naturally more interested in relief of their suffering than in surveys.

Finally, the speaker summed up his impression of the feeling in France toward the Nazis, the English and the Americans. Apparently the majority of the population is grateful for the assistance of America, intensely hates the Nazis, and is willing to become allied with any enemy of theirs.

Dr. W. D. Robinson, who was on a similar mission to Madrid, compared his observations with those of Dr. Stuart. In Spain, the deprivation has been going on for a longer time, and reconstruction has been hindered by the persistence of intense lack of unity. Rations are about as in France, but an active bootleg trade alleviates matters somewhat, at least for the financially fortunate, and a great deal more food can be obtained from the United States, where there is only one border to be crossed. The native diet was found particularly inadequate in calories, protein, calcium and vitamin B. Vitamins A and C levels were adequate during the summer months when the survey was made, for at that time there were sufficient green vegetables. Although little classic deficiency disease was encountered, the children were definitely retarded, and conditions were reported worse in southern Spain. The nutritional outlook is dismal, for the grain crops do not appear promising, the Spanish government is trying unsuccessfully to be self-sufficient, and the relief agencies are being continually thwarted by the administration.

In reply to a question whether food was entering unoccupied France from the Nazis as a result of their collaboration pact, Dr. Stuart stated that exactly the opposite was taking place. Furthermore, the 100,000 prisoners returned to France as part of the same agreement were the physical and mental derelicts who were merely a burden to Germany and less than no help to the disil-

lusioned French people. In conclusion, Dr. Stuart pointed out that the most pressing immediate problem is an emotional rather than a nutritional one, but that the real work in the nutritional field is the surest way of building up the necessary morale.

#### BOSTON LYING-IN HOSPITAL JOURNAL CLUB

At a regular meeting of the Boston Lying-in Hospital Journal Club held at the hospital on October 30, Dr. Norris Vaux, of Philadelphia, spoke on "Some Local Uses of Estrogenic Hormones in Obstetrics and Gynecology."

This method of therapy was undertaken for several reasons. In the first place, in certain conditions and patients, the local tissues respond poorly if at all to parenteral injection of these hormones. Furthermore, the local application of the effective hormone has the advantages of easier use, a better concentration, a prompt effect and less systemic reaction. The conditions in which this mode of therapy has found favor include gonococcal vulvovaginitis in children, postmenopausal atrophic vaginitis, and hypoplastic and aplastic breasts and vulvas in young women.

In general, in the vaginal cases, a highly aqueous, acid solution of one of the estrogenic hormones is used. Besides the well-known increase of cornification of the vaginal mucosa, this increase of acidity adds another beneficial factor. Other forms of application have been suppositories and jellies with pH 4. In certain cases, mild antiseptics are added to the liquid or other medium and are thought to have certain definite advantages. It is actually a combination of two recognized forms of treatment. The antiseptic serves to control temporarily the sepsis until the hormone is effective. Smaller dosages of the hormone then become effective, which is a particularly important consideration in immature girls, in whom larger doses might cause premature development or unpleasant symptoms. Finally, it has been demonstrated that the inclusion of antiseptics does not inhibit the action of the hormones.

This form of therapy has been employed in the rather unusual syndrome of atrophic vaginitis in young adult women, in which the vaginal mucous membrane is thin, shiny and often ulcerated. Bacteriologic studies reveal mixed flora, and the persistent discharge is invariably found to be alkaline. The epithelial cells contain no glycogen. The menstrual cycle is usually only slightly disturbed, whereas the urinary estrogen values are more or less normal. As might be expected from these observations, the vaginal mucous membrane responds only to large doses of hormone. The use of 5-mg. suppositories of stilbestrol brought about clinical improvement, without any change of the menses but with noticeable changes of the vaginal mucous membrane. Withdrawal of the hormone caused an exacerbation of all symptoms and seems to indicate that continuous treatment is necessary to alleviate the symptoms.

In cases of pruritus vulvae and kraurosis, enormous doses were necessary to procure the desired effect. For this purpose, stilbestrol in oily form was dissolved in a vanishing-cream base, with from 10 to 100 mg. of the hormone to the 30 cc. of cream. About 4 gm. of this preparation was then daily applied to the affected area.

Certain cases of atrophic breasts have been found to respond to local therapy when other methods have failed. Here again stilbestrol in a vanishing-cream base has proved the most convenient and effective form of treatment. The addition of equal amounts of testosterone



as it displaces lipids and thus protects the liver stores. It was found that the most satisfactory means of obtaining these protein levels was by forced feeding, and that voluntary feeding, in addition to the parenteral use of glucose, was far superior to the latter alone. The most suitable protein so far found is casein, which is abundant in cottage cheese. Also used are Casec and protein digests, but the widely advertised gelatin is far inferior. That the additional protein must be suitable was demonstrated by feeding beef heart to animals and thereby actually increasing rather than decreasing the lipid content. If only the parenteral route is available, glucose and plasma are most effective, but nothing has been found to equal oral feedings. Despite already existing liver damage, every patient can be improved preoperatively by an adequate diet.

The indications for common-duct exploration are essentially those in common usage, but it is believed that this procedure should be carried out oftener. When such an operation is properly performed in competent hands, the mortality should not be materially higher than in the simple operation. Postoperatively, however, the draining bile should not be wasted even if the bile-salt concentration is low, for it is in this way that asthenic states develop, probably because of the extrahepatic importance of bile. A simple method for overcoming this difficulty is to connect a drainage bottle at the same height as the duodenum and thus cause the bile to flow into the gastrointestinal tract.

Postoperatively, the diet also plays a significant role, and the same principles apply as in the preoperative management. The best regimen is still unknown, but protein is certainly necessary. Carbohydrate aids only so far as it allows endogenous protein to be freed for use in regeneration of liver. In dogs, the best regeneration was noted when the protein fed contained 25 per cent liver.

Vitamin K therapy should be resumed postoperatively and continued until wound healing is assured. The blood values may and probably do fall after operation, so that preoperative values are not significant. Patients who fail to respond to such therapy before operation will not respond afterward, and should therefore receive blood or plasma. The T tube is never removed until a cholangiogram has been carried out, for even the best surgeons have been known to overlook a stone at operation. The mortality in common-duct explorations at Dr. Ravdin's clinic has decreased from 22 per cent in 1922-1929 to 11 per cent in 1935-1938, and to 2.6 per cent in 1938-1941. In the last 629 consecutive nonjaundiced patients operated on, there has been only one death, and this includes all types of biliary surgery.

The discussion was opened by Dr. Charles G. Mixter, of the Beth Israel Hospital. He favors cholangiography on the operating table at the time of operation. The closed method consists in inserting dye into the common duct through a ureteral catheter in the cystic duct, without opening the former. This is employed in questionable cases of small stones and apparently normal ducts, for common-duct exploration is believed to increase the morbidity and also the mortality in any but the most competent hands. The second type of cholangiogram is that taken through the T tube following exploration but before the patient leaves the table. Eighty-five of 88 cases of the latter type were satisfactory, and 75 came out as expected. Six residual stones were found, but in only 3 cases were they removed; the patient's condition did not warrant removal in the others. The type of patient that affords the greatest problem at present is the one with residual symptoms following operation and with a normal common duct. Some patients with so-called "dyskinesia" find relief from antispasmodics, but those with severe

usually not relieved. Dorsal sympathectomy, including the splanchnic nerves, offers some promise in such case but the series is as yet too small to draw any conclusions.

Dr. Chester M. Jones, of the Massachusetts General Hospital, emphasized the value of clinical evaluation for diagnostic purposes, but stated that liver-function tests have a place in following the progress of certain cases. On the whole, medical cases differ from surgical ones in that there are fewer cells for regeneration. Cases were cited in which surgery is eventually necessary but is contraindicated at the onset. Since jaundice in the presence of stones usually indicates poor liver function and since the stones may not be the cause of the jaundice, the patient should not be approached surgically so long as bile is reaching the gastrointestinal tract. Patients with high dye retention and slight jaundice are also poor risks, and liver tests are of some value in such cases. The diabetes associated with biliary-tract disease is invariably mild, and the removal of a diseased gall bladder and stones makes it even more so. Dr. Jones believes that the greatest risk in cardiac patients with biliary disease is leaving them alone. Esophageal hernia may give rise to similar stimuli, which are probably afferent to the heart without passing through the splanchnic nerves. Vitamin K may be used as a measure of liver insufficiency and often fails to cure or aid medical cases. It is now known that whole blood, but not pooled, contains prothrombin and thus aids in establishing normal levels.

## BOOK REVIEW

*Oral Pathology: A histological, roentgenological, and clinical study of the diseases of the teeth, jaws, and mouth*. By Kurt H. Thoma, D.M.D., and Charles A. Brackett, D.M.D. 4°, cloth, 1306 pp., with 1370 illustrations, including 137 in color. St. Louis: The C. V. Mosby Company, 1941. \$15.00.

Although the title of this work suggests a study of the pathologic findings in oral disease, it also represents a clinical study of disease of the teeth, jaws and buccal mucosa, with radiographic findings and excellent histologic illustrations.

The forty-five chapters include studies of hereditary, hormonal and nutritional influences in the development of the teeth and jaws, together with experimental pathology. In the latter subject, there has been the greatest progress in the study of oral disease in recent years. A review of the subject of dental caries based on an enormous literature is presented, with extracts from the more important articles and with a special reference to experimental work. The chapter on periodontal disease, with modern classification of the many lesions, helps to simplify the terminology of the subject. Diseases and tumors of the jaw are dealt with in a manner similar to that in a previous book, *Clinical Pathology of the Jaws*, published a few years ago. Chapters on diseases of the oral mucosa, lips, tongue and salivary glands are especially well illustrated in color.

The bibliography, which is very complete and up to date, includes the important articles in the foreign literature.

This volume is the most complete of its kind in the American literature, and its compilation is a result of many years of study of oral disease on the part of the authors. Disease of the oral cavity has been a neglected field in medicine, and this work should be of equal interest to the medical clinician, the oral surgeon and the clinical dentist. A knowledge of oral disease is valuable to both the medical and the dental practitioner, since the oral cavity may be considered the mirror that reflects the presence of disease elsewhere in the body.

# The New England Journal of Medicine

Copyright 1942 by the Massachusetts Medical Society

VOLUME 226

FEBRUARY 26, 1942

NUMBER 9

## THE TREATMENT OF MAMMARY PAIN AND SECRETION WITH TESTOSTERONE PROPIONATE\*

IRA T. NATHANSON, M.D.,† JOE V. MEIGS, M.D.,‡ AND LANGDON PARSONS, M.D.§

BOSTON

CERTAIN syndromes in women before the menopause are characterized by mammary swelling and pain, with or without secretion from the nipple. They are undoubtedly present in a large percentage of cases, but may vary considerably in their intensity and extent. Many women have obvious changes in the breasts and may never be aware of any abnormality until it is found on routine examination, whereas others with minimal changes may have marked subjective manifestations. Hence, it is sometimes extremely difficult to distinguish the syndrome from what is considered a normal variation. Only patients with pronounced lesions seek consultation with a physician, either for relief of symptoms or because of fear of cancer. These patients, who have unequivocal signs and symptoms, are discussed in this paper.

The lesions are generally classified under the generic term of "chronic cystic mastitis," but should be grouped under more specific terms because they represent fairly distinct clinical and pathologic entities. The changes are believed by most observers to be due to a sex-hormone imbalance whose nature is not clear. Treatment of these syndromes with estrogenic hormone on the assumption of an estrogen deficiency was first suggested by Cutler.<sup>1</sup> Others have since reported varying success from treatment with more active preparations of the same hormone. It is the purpose of this communication to record our experience in the treatment of these lesions by the use of the male sex hormone, testosterone. The rationale of therapy with testosterone is based pri-

marily on experimental data in animals, which suggest that relatively prolonged administration of the hormone not only reduces the secretory activity but also may reduce the number of cells of the breast epithelium, especially those in a hyperplastic process. Further evidence suggests that an action on the vascular bed of the breasts may relieve the venous congestion and edema so often seen in these patients. It is our belief that excess secretion, increased vascularity and edema are usually responsible for the swelling and pain, and that the symptoms and signs abate only after resorption of the fluid or a diminution in the venous engorgement. Therefore, testosterone, because of its action, should be effective in the treatment of these syndromes.

A thorough clinical and experimental study has been carried out for the last six years in the cases reported below, which were selected from a much larger group. Several of our observations have been recorded,<sup>2</sup> and others, particularly those concerned with the mechanisms of the syndromes, will be published soon. In the evaluation of any type of therapy in these lesions, it is imperative to select the patients with care so that an accurate clinical appraisal of the results can be made. Cases were therefore chosen on one or more of the following criteria: frequent examination without treatment by the same examiner for a long time, so that the possibility of a psychogenic element or a spontaneous remission (both of which are not uncommon) could be minimized; severity of the syndrome and presence of unquestionable physical findings, such as marked nodularity and secretion, so that any change would easily be recognized; failure to control the symptoms with a suitable breast support or with a placebo, or after estrogenic therapy; absence of demonstrable pelvic disease or removal of such disease without re-

\*From the Surgical Clinic of the Collis P. Huntington Memorial Hospital, Harvard University and the Tumor Clinic of the Beth Israel Hospital.

†Instructor in surgery, Harvard Medical School; assistant surgeon, Collis P. Huntington Memorial Hospital and Beth Israel Hospital.

‡Instructor in surgery, Harvard Medical School; associate surgeon, Collis P. Huntington Memorial Hospital.

§Assistant in surgery, Harvard Medical School; assistant surgeon, Collis P. Huntington Memorial Hospital.

lief of symptoms, since these processes are frequently related; intelligence of the patient, so that reasonably reliable information about the subjective symptoms would be available.

### CLASSIFICATION OF LESIONS

We distinguish two main groups—adenofibrosis and nonpuerperal mammary secretion—with

the first group, the symptoms may abate at the menses. The discharge may be serous or may resemble colostrum, and may be of varying degrees of viscosity. Examination usually reveals dilatation of the ducts, especially near the areola, and slight nodularity elsewhere in the breast. The breast tissue itself is ill-defined, and the nipples are frequently crusted. If secretion is not obvious,

TABLE 1. *Incidence of Symptoms and Physical Findings.*

SYMPTOM	TOTAL NO. OF CASES	CASES WITH SYMPTOMS			CASES WITH PHYSICAL FINDINGS		
		PAIN	SWELLING	SECRETION	DILATATION OR NODULARITY OF DILATED DUCTS	SECRETION	
Adenofibrosis . . . . .	9	9	7	0	7	9	0
Nonpuerperal mammary secretion . . . . .	21	10	15	5	10	21	21

various gradations and do not include obvious cystic disease or isolated lumps or nodules (Table 1).

*Adenofibrosis.* The patients in this group have cyclic swelling and pain in the breast, usually in the premenstruum, but without obvious or demonstrable secretion. The relief that usually ensues with the onset of the menses is dramatic. On examination, two extreme types are distinguishable, but many present intermediate variations.

*Type I.* There is an increase in density of the entire mammary gland, which is well differentiated from the overlying skin, the subcutaneous tissues and the underlying structures. The gland is firm, and usually resembles a saucer or disk in its configuration. These changes as seen in histologic sections are due to an increase in the stroma, without obvious changes in the ducts or acini. During the premenstruum, there is frequently venous engorgement, as well as edema.

*Type II.* This resembles the first type, especially in the density of the gland. In addition, there is a diffuse, fine or moderate nodularity throughout the breast but usually most prominent in the upper outer quadrant. Histologically, there is an increase in the number of acini, as well as an increase in the fibrous tissue, with the usual edema.

Either of the types may show hyperplasia and, sometimes, dilatation and secretion within the acini. Semb<sup>3</sup> has referred to these entities as adenofibrosis, and Dawson<sup>4</sup> as adenositis. Taylor and Waltman,<sup>5</sup> in a detailed study, have recently presented an excellent description of these syndromes.

*Nonpuerperal mammary secretion.* The salient feature of this type is discharge, usually accentuated before the menses and sometimes associated with swelling and cyclic or acyclic pain. As in

removal of the crust, with gentle pressure on the ducts, results in the escape of fluid from the nipple. On gross and microscopic examination, the ducts are dilated and contain secretion and, sometimes, inspissated material. Hyperplasia of the duct and acinar epithelium, with edema in the supporting tissue, is evident. We have termed this the nonpuerperal secretory type of breast, a designation also utilized by Taylor and Waltman.<sup>5</sup> This group probably falls into the type designated as mazoplasia by Cheate and Cutler<sup>6</sup> and epitheliosis by Dawson.<sup>4</sup>

Many of the cases include features of both the above groups, and may be placed in a third class. However, for the purpose of clarity in this communication, the lesions have not been classified further. All cases with secretion are placed in the first group, in spite of the fact that they may show some of the manifestations of the second.

### METHOD OF TREATMENT

The chief preparation used was testosterone propionate.\* In a few cases, testosterone made up in a lanolin base was utilized as an ointment. Ten mg. of testosterone propionate in 1 cc. of sesame oil was given intramuscularly every other day, beginning about two weeks prior to the expected period. If the symptoms were of long duration during the cycle, treatment was started at least a few days before the onset of the expected symptoms and continued up to the period. In the more intractable cases, the hormone was given every other day throughout the cycle, except during the period of flow. At times, the dose level was increased to 25 mg. In any event, the maximum amount given during any single month was 250 mg., but the usual dosage varied between 75

\*We are indebted to Drs. Gregory Stragnell and Max Gilbert of the Schering Corporation, Bloomfield, New Jersey, and to Dr. Ernst Oppenheimer of the Ciba Pharmaceutical Products, Incorporated, Summit, New Jersey, for generous quantities of testosterone propionate supplied under the trade names of "Oreton" and "Perandren."

and 150 mg. If the hormone was administered percutaneously in the form of the ointment, the patient was instructed to rub the equivalent of 2 to 4 mg. into the skin of each breast before retiring. The total dosage was therefore 28 to 56 mg. a week. Although the amount used by injection was approximately the same as that given intramuscularly, the relative effect of each route is probably different. The percutaneous method, as contrasted to parenteral administration, aims at a more direct action on the breast, with less systemic effect. Since the exact mechanism of action of the hormone on the breast is in doubt, it is not known at present if any one method is to be preferred. However, Salmon et al.<sup>7</sup> are of the opinion that testosterone if properly used is equally effective by any route. In this series, injection was reserved for patients who could not report regularly for injections.

Treatment was never continued for more than three consecutive months in any given case without a rest period of one to several months before resumption. When the larger dosages were used, the maximum length of any single period of treatment was two months. The importance of these rest intervals is pointed out below. It was seldom necessary to give more than two courses of therapy to evaluate the results.

#### COMPLICATIONS OF TREATMENT

Overdosage with testosterone in women produces undesirable side effects, such as hirsutism, enlargement of the larynx with deepening of the voice, acne and enlargement of the clitoris. With the dosage used in our series, 2 patients developed mild hirsutism, and 1 developed moderately severe acne. These effects regressed rather rapidly when treatment was discontinued. It is for this reason that we do not continue treatment too long. We are of the opinion that prolongation of the treatment rather than the dose level is the significant factor in the production of undesirable side effects. As much can probably be accomplished by a definite routine of treatment of two or three months, followed by a rest period for a month or more before resuming the medication to allow for partial regression of the undesirable effects of the hormone. It seems likely that each course of treatment will produce some regression of the breast lesions and that if the interval without treatment is not too prolonged, recurrence will not reach the pretreatment state. In this way, the drug can be used more safely and probably as effectively. It should be emphasized that the hormones available at present are potent, and that a safe dosage for one person may be excessive for

another, because of individual susceptibilities and responses. To avoid the side effects, one should treat each patient with these factors in mind. It is extremely interesting, however, that treatment did not alter ovarian function, since 2 patients in this group subsequently became pregnant, delivered normal babies and had normal lactation. Furthermore, with the dosage used, no effect on the menstrual cycle, with the exception of an occasional delay for a week, was noted in any case. Larger dosages would undoubtedly have caused a temporary suppression of the menses in some patients.

#### RESULTS

The treatment of these syndromes with testosterone was first suggested by Desmarest and Capitan,<sup>8</sup> who reported favorable results in 16 of 17 treated cases. They concluded that the hormone suppressed the congestion preceding the menses, decreased or inhibited the development of further disease, and caused regression of the nodules. Others<sup>9-11</sup> later published similar observations. Spence<sup>10</sup> and Atkins<sup>11</sup> stressed the psychogenic element in certain patients who present themselves with mammary pain. The former injected olive oil in 24 patients, 13 of whom had "dramatic relief." The latter, in a series of 212 patients, found that 31 had relief after the administration of inert pills or the injection of oil. He stated that these patients must have consisted largely of those in whom a psychologic factor predominated, although some undoubtedly had a spontaneous remission. However, 16 patients in Spence's series were considered to have a definite indication for treatment. Ten of 12 with pain were improved or completely relieved, and 8 of 12 with nodularity showed regression after treatment with testosterone. Atkins selected 34 patients as suitable for treatment, and 25 of these showed improvement. The degree of regression of symptoms and signs paralleled the total dosage and the period during which treatment was employed. Atkins concluded, however, that much of the beneficial effect on the breast was vitiated by a fairly high percentage of undesirable side effects. Geist et al.,<sup>7</sup> in a recent publication, noted improvement in 6 of 10 patients with premenstrual pain and in 2 of 4 patients with cystic nodular breasts.

It can be seen from Tables 2 and 3 that in our series testosterone propionate was effective in the treatment of mammary pain and secretion. All the patients with adenofibrosis were improved or completely relieved of their symptoms. In 7, an improvement in the physical findings was beyond any question. Of 21 patients with mammary se-



cretion, 18 were subjectively improved or completely relieved. It is interesting that secretion was completely inhibited during the period of treatment in 13 patients.

The results of therapy with testosterone seem significant, since 11 of the entire group had been previously treated, without success, by estrogenic hormone, and the remainder had had a placebo either orally or by injection, or fell into one or more of the criteria outlined above. This, therefore, in spite of obvious physical findings, further

TABLE 2. *Results of Testosterone Therapy in 9 Patients with Adenofibrosis.\**

THERAPEUTIC RESULT	REGARDING SYMPTOMS	REGARDING PHYSICAL SIGNS
Complete relief	6	0
Improvement	3	7
No change	0	2

\*Of 3 cases previously treated unsuccessfully with estrogens, all had symptomatic relief and improvement in physical findings.

eliminated patients who might possibly have had a neurosis or spontaneous remission. Consequently, these observations are in accord with those of other investigators.

The most obvious clinical change after treatment was a reduction or inhibition or premenstrual swelling that was easily observed by the patient and the examiner, even though gross secretion or localized areas of tenderness and pain persisted.

TABLE 3. *Results of Testosterone Therapy in 21 Patients with Nonpuerperal Mammary Secretion.\**

THERAPEUTIC RESULT	REGARDING SYMPTOMS	REGARDING PHYSICAL SIGNS	REGARDING SECRETION
Complete relief	12	3	13
Improvement	6	15	5
No change	3	3	3

\*Of 8 patients treated unsuccessfully with estrogens, all but 2 had complete relief or improvement in symptoms and physical findings.

Although there was complete relief from symptoms or secretion, in many cases the physical signs improved but did not disappear completely. This improvement was manifested by softening, a decrease in nodularity and even a reduction in the size of the breast. When not completely inhibited, the secretion was reduced or exhibited gross alterations. Many patients volunteered the information that it was necessary to use a smaller brassière. We consider this to be an important observation in the evaluation of the therapy, since it signifies that the major symptoms had been relieved.

Recurrence of symptoms and physical signs was the rule after treatment was discontinued. Few patients had relief after six months, and many

had recurrence within the first few months after treatment was stopped. However, with recurrences, the symptoms were usually less severe, and the findings were not so pronounced as they had been in the pretreatment period. Some of the patients were given further courses of treatment, with satisfactory results, but to date few have continued to remain completely free of symptoms. Therapy of a more rigorous nature for longer periods might have given permanent relief. It is questionable, however, whether one would be justified in such an attempt, because of possible undesirable generalized or local side effects. As stated above, regardless of individual idiosyncrasies, these effects are usually in proportion to the amount and the period over which the hormone is given. It is our opinion that proper administration of the hormone can produce the desired therapeutic result without reaching the threshold for other manifestations. This has been well demonstrated by Geist and Salmon,<sup>12</sup> who made careful observations on a large series of patients treated with testosterone for various endocrine disturbances. In our series, except in a few cases, the dosage and time interval appeared to be below the threshold level for the production of undesirable changes. In this respect, therefore, our findings differ from those of Spence<sup>10</sup> and Atkins,<sup>11</sup> who usually employed large amounts of the hormone for a longer time.

It can be demonstrated histologically that testosterone is capable of reducing the number of cells and the activity of the epithelium in the breasts of animals<sup>13</sup> and, to a lesser extent, in human beings.<sup>11</sup> The mechanism by which the clinical and laboratory changes are produced is not clear. It is commonly recognized that the estrogenic hormone, if not properly balanced, results in hyperplasia of the breast epithelium. However, it has not been established whether this is a direct effect or one that is mediated through the anterior hypophysis, presumably by increasing the activity of the mammogenic hormone, which is believed by many to be the stimulating factor in epithelial growth in the breast. Another hormone of the anterior hypophysis—prolactin—is probably responsible for secretion and lactation. In experimental animals and in human beings, it has been shown that testosterone may counteract the action of the estrogens. It may also inhibit secretion and lactation, probably by preventing the activity of prolactin on the breast itself, or through its action on the pituitary gland. Therefore, since it is probable that these mammary dyscrasias are due to a hormonal imbalance, it seems likely that the beneficial effects of testosterone may be ac-

complished by establishing a balance or by counteracting the action of the other hormones that are probably involved in the process. This balance in itself may result in an alteration of the vascular bed of the breast, which in turn may be the sole factor in the reduction of venous congestion, edema, epithelial elements and secretion. At present, it is difficult to say whether these effects of testosterone are due to a direct action on the breast or to an indirect one mediated through other organs.

Finally, it should be stressed that this treatment must be reserved for patients in whom there is not the slightest doubt concerning the presence of cancer, or any evidence of an isolated tumor, or bleeding from the nipple.

### SUMMARY AND CONCLUSIONS

Testosterone propionate was administered to 30 carefully selected patients with severe mammary pain and secretion. It was found to be an effective agent in the relief of the syndromes in a high percentage of cases. It appears to be more efficacious than the estrogenic hormone in the treatment of the same lesions. Recurrence of symptoms and signs is the rule, usually within six months

after medication is discontinued. Prolonged and continuous treatment, especially with large doses, is to be discouraged. As much as can be accomplished by planned periods of treatment followed by adequate rest intervals. Many patients present a predominant psychogenic element, and others have spontaneous remissions, therefore, care should prevail in the selection of the case for this or any similar type of therapy.

### REFERENCES

1. Cutler M. The cause of painful breasts and treatment by means of ovarian residue. *J A M A* 96:1201-1205, 1931.
2. Rogers H and Nathanson I T. Chronic cystic mastitis: practical management in a cancer clinic. *New Eng J Med* 212:581-586, 1935.
3. Semb C. Pathologic anatomical and clinical investigations of fibroadenomatous cystic mammae and its relation to other pathological conditions in mamma especially cancer. *Acta chir Scandinav* (suppl 10) 64:1-484, 1928.
4. Dawson E K. Carcinoma in mammary lobule and its origin. *Edin Surg M J* 40:37-83, 1933.
5. Taylor H C Jr and Wailman C L. Hyperplasia of the mammary gland in the human being and in the mouse. *Arch Surg* 40:733-820, 1940.
6. Cleattle G L and Cutler M. *Tumours of the Breast: Their pathology, symptoms, diagnosis and treatment*. 596 pp. London: Edward Arnold Co, 1931.
7. Geiss S H, Salmon U J and Hymen E C. Androgen therapy in the human female. *J Clin Endocrinol* 1:154-186, 1941.
8. Demarest E and Capita N. Mms. Le traitement des mastopathies par l'acétate de testostérone. *Presse méd* 45:777-9, 1937.
9. Loesser A A. The action of testosterone propionate on the uterus and breast. *Lancet* 1:373, 1938.
10. Spence, A W. Testosterone propionate in chronic mastitis. *Lancet* 2:870-873, 1939.
11. Adkins H J B. Treatment of chronic mastitis. *Lancet* 2:411-413, 1940.
12. Geiss S H and Salmon U J. Androgens. *J A M A* 117:2207-2213, 1941.
13. Nathanson I T. Unpublished data.

## A COMPARISON OF BLOOD PROTHROMBIN LEVELS WITH STANDARD FUNCTION TESTS IN DISEASES OF THE LIVER

FRANKLIN W WHITE, MD,<sup>1</sup> ENRIQUEL DEUTSCH, MD,<sup>2</sup> and STEPHEN MADDOCK, MD.<sup>3</sup>

BOSTON

IN 1935, Quick<sup>1</sup> introduced a simple interpolative method for measuring the amount of prothrombin in the blood. This proved an invaluable guide in the indications for treatment of vitamin K deficiency. The experimental work associated with the discovery of vitamin K<sup>2,3</sup> suggested that the liver was important in prothrombin production. When it was found that persons with a damaged liver often responded poorly to vitamin K treatment,<sup>4-7</sup> efforts were made to expand the use of the prothrombin test to the status of a liver-function test.

A possible correlation between prothrombin and liver function tests has been suggested by early reports.<sup>8,12</sup> In 1939, Wilson<sup>8</sup> remarked

The quantitative level of the plasma prothrombin was found to correlate closely with the quantity of hippuric acid excreted . . . [and that] the quantitative levels of plasma prothrombin and the amount of hippuric acid excreted following the ingestion of a known quantity of sodium benzoate would seem to have reflected most sensitively and consistently the degree of liver damage existing.

Stewart and Rourke,<sup>9</sup> in 1939, suggested that further study might reveal that the prothrombin depression is a better index of liver damage than other standard liver function tests.

Pohle and Stewart,<sup>10</sup> in 1940, observed, "The present studies suggest that in the absence of obstructive jaundice, external biliary fistula or an abnormal intestinal absorptive surface, the plasma prothrombin concentration serves as a measure of liver function."

Andrus,<sup>12</sup> in 1941, considered one of the most fruitful fields of the study of vitamin K to concern its use in the investigation of liver function;

<sup>1</sup>Read at the fifty-sixth annual meeting of the Association of American Physicians, Atlantic City, May 6, 1941.

<sup>2</sup>From the Second and Fourth (Harvard) Medical Services and the Surgical Research Laboratory, Boston City Hospital.

<sup>3</sup>Consulting physician, Boston City Hospital.

<sup>4</sup>Fellow in surgical research, Boston City Hospital.

<sup>5</sup>Director of surgical research, Boston City Hospital.

he believes that such a test "possesses certain advantages over even the best of the current tests of liver function."

On the other hand, two recent papers<sup>13, 14</sup> have shown little or no correlation between the hippuric acid excretion test and blood prothrombin levels either before or after the administration of vitamin K in adequate doses. Because of these discrepancies, it seems worth while to present the results in a series of cases of liver disease encountered as routine diagnostic problems on the wards of a large hospital, without reference to the type of disease presented, and to compare the results in an impersonal way.

The material consists of 100 unselected cases of liver and biliary-tract disease in which about 700 tests were made. The prothrombin percentage and its response to vitamin K in adequate doses were compared with the excretion of hippuric acid and urobilinogen in the urine, and fractional bromsulfalein elimination from the blood. For the sake of simplicity, this paper is confined largely to a comparison of the prothrombin level with the hippuric acid excretion.

#### METHODS

Hippuric acid excretion in the urine was determined, following oral administration, by the gravimetric method of Quick.<sup>15</sup> The prothrombin time was measured by the Quick<sup>1</sup> technic, and converted to the percentage of normal blood prothrombin by reference to a curve obtained according to the method of Kark and Lozner.<sup>16</sup> The hippuric acid excretion test was usually performed on the day that the blood prothrombin level was estimated or within three days (seventy-two hours) of that time.

The urobilinogen in the urine was estimated by the Wallace and Diamond procedure,<sup>17</sup> and the bromsulfalein retention by a fractional method,<sup>18</sup> using 2 mg. of bromsulfalein and testing the blood at the end of five and fifteen minutes. Some of the various tests were repeated four or five times in all cases and, in some cases, up to ten and twenty times.

The preparations employed for restoring vitamin K were either 2-methyl-1,4-naphthoquinone, in 1-mg. doses orally each day or 3.2-mg. doses of 2-methyl-1,4-naphthoquinone-3-sodium sulfonate intramuscularly once in four or five days. Patients with high or normal blood prothrombin levels were not given vitamin K preparations. All patients received the currently accepted treatment for liver damage—that is, a high-carbohydrate, normal-protein and low-fat diet, and oral or intravenous glucose solutions, thiamin and nicotinic

acid fortified with other vitamins and occasionally reinforced with parenteral liver extract.

#### RESULTS

##### *Correlation of Tests*

A definite lack of correlation between the prothrombin level and hippuric acid excretion was found in a large number of cases (Table 1). Hippuric acid excretion was often much below the normal level of 3 gm., whereas the prothrombin level varied from low to normal in different cases.

There are two ways of using the prothrombin level as a clinical test: either as an index of vitamin K deficiency on admission or as one of response to vitamin K treatment on the part of the patient. The second is much more valuable, since the variable factor, the amount of vitamin K available, is removed. The prothrombin levels on admission may be within the same range, but the response to vitamin K treatment best brings out the differences that are found in various types of liver disease.

##### *Discovery of Liver Damage*

In the severest type of liver damage (acute diffuse necrosis), all the recognized liver-function tests used were found to be positive. In cases of intermediate severity, such as the cirrhoses, these tests varied greatly in the proportion of cases giving a positive response. In our previous experience<sup>18-20</sup> and in the present examination of this group of cases, the percentage of initial abnormal tests in cirrhosis is approximately as follows: oral galactose tolerance, 25 per cent; cholesterol ester, 45 per cent; prothrombin, 53 per cent; urobilinogen in the urine, 77 per cent; hippuric acid excretion, 88 per cent; and fractional bromsulfalein excretion, 91 per cent. The prothrombin time holds an intermediate position as an index of liver damage. In the milder types of hepatic dysfunction, some tests were always negative, but others, such as the hippuric acid excretion and the fractional bromsulfalein elimination, were positive in nearly all cases. The prothrombin level was normal in 47 cases in this series at the time of admission, and below normal in 53 cases. Pohle and Stewart<sup>10</sup> found 47 per cent below normal in a similar group of 136 cases.

Table 2 lists the total number of cases with abnormal prothrombin levels before and after treatment. In 53 cases, the prothrombin level was abnormal on admission; the hippuric acid excretion was abnormal in 83 cases. In cases of acute hepatitis, a low prothrombin level quite often returns to normal after active glucose and fluid therapy without giving vitamin K analogues (Table 1. Cases 24, 58 and 59).

TABLE 1. Summary of Data on All Cases.

CASES WITH NORMAL INITIAL PROTHROMBIN LEVELS							CASES WITH LOW INITIAL PROTHROMBIN LEVELS						
CASE NO	PROTHROMBIN LEVEL	HIP PURIC ACID EXCRETION	BROMSULFALEIN RETENTION	UROBILINOGEN EXCRETION	REMARKS		CASE NO	PROTHROMBIN LEVEL	HIP PURIC ACID EXCRETION	BROMSULFALEIN RETENTION	UROBILINOGEN EXCRETION	REMARKS	
			5 min 15 min								5 min 15 min		
	% gm	%	%	post dil				Before treatment %	After treatment %	Change %	gm %	% post dil	
CHRONIC HEPATITIS (CIRRHOSIS)													
3	100	2.0	70	20	32		1	52	56	+4			
4	100	2.0	90	20	2		2	30	50	+20	12	65 60	
26	100	2.5	40	15	16		5	24	40	+16	2.6	60 40 256 32	
29	100	1.3	55	10			6	50	60	0	1.4	100 85 4	
30	100	1.0	30	10			7	45	51	+6	0.1	128 64	
33	90	1.4	100	30	64 64		8	50	40	-10		64 128	
34	95	1.5	70	15	256 64	Patient died	9	45	46	+1		5 mg *	
35	100	0.4	80	65	16	Patient died	10	27	32	+5	1.1	100 90 40 80	
39	80	Low	100	50	2.8 mg *		11	30	39	+9	0.8	100 45 32 64	
40	81	1.7	40	5	16	Patient died	12	50	33	-17	1.5	80 40 16 16	
41	90	2.5	50	5	128		13	44	39	-5	1.7	64 37	
42	100	0.9			32		28	60	48	-12	2.0	256	
44	100	1.1			256 32		31	48	45	-3	1.7	64 128	
46	100	0.6					37	43	70	+27	2.0	128 2	
48	80	1.0					36	45	60	+15	1.4	32 512	
50	90	2.0	60	45	16 16		43	54	60	+6	0.7	256 64	
51	100	2.3			4		45	70	8	+8	Low	100 5 32	
52	100	0.5	60	35			47	30	62	+32	0.5	32 4	
54	100	1.6					49	38	33	-5	1.0	90 45 8	
66	100	2.0	70	10	128 64		53	50	90	+40†	1.4	50 30 0	
67	100	1.4	80	65	64 64		55	28	37	+9	0.3	90 60 32 128	
77	98	1.3	50	30	128 32		90	65	70	+5	2.5	15 10	
83	100	0.5	100	95			91	62	68	+6	3.8	5 Tr 16 4	
84	80	3.6					94	40	40	0	1.1		
86	80	1.6	35	10	128		95	40	40	0	1.2		
92	96	2.7					97	60	60	0	1.3		
100	100	2.0	40	25			98	65	65	0	1.0		
ACUTE HEPATITIS													
56	100	1.0	100	45	64 16		14	42	23	-19	0.7	0 0	
57	100	2.0			8 8		15	35	80	+45	1.7	100 80 64 16	
61	98	1.1			8 16		16	40	100	+60		4 0	
85	82	0.5	10	0		Patient died	17	68	29	-39	1.3	0 64	
							24	32	100	+68	1.5	65 40 0 4	
							58	30	100	+70	1.1	20 5 32 16	
							59	52	100	+48	2.8	40 10 0 32	
							60	56	80	+24	1.3		
							87	71	95	+24	0.4		
							88	40	23	-17	1.3	2 1	
							93	20	23	+3	0.7		
							96	36	40	+4	1.3		
OBSTRUCTION OF COMMON DUCT													
38	80	1.6			32	Cancer	18	60	62	+2		0	
64	100	1.4			32, 32	Gallstone	19	75	100	+25	0.4	2	
65	100	2.0			4, 0	Cancer							
68	85	1.2			80 0	Cancer	20	45	100	+55	1.4	0	
69	95	1.2			0	Cancer	21	15	100	+85	2.0	85 30 0	
							22	20	100	+80	1.0	2 2	
							23	20	100	+80	1.0	100 80 8	
							25	16	73	+57	0.8	128 0	
							67	24	39	+15	1.5		
							99	30	100	+70	0.4	0	
TUMORS OF LIVER AND SO FORTH													
13	83	4.2	20	5		Hodgkin's disease	76	67	70	+3‡	1.3	30 20 16 4	
37	100	1.7	100	80	128	Cancer patient died	80	70	99	+29	1.1	Cancer patient died	
63	100	2.8				Blood dyscrasia	81	31	100	+69	1.3	30 Tr	
75	100	0.5			16	Cancer							
78	86	2.0			8 0	Cancer							
79	100	2.5				Cancer							
87	98	0.3				Cancer patient died							
89	92	2.2	20	5	8	Cancer?							
GALLBLADDER DISEASE													
70	100	1.1	30	15	128		71	44	53	+9	2.1	40 20 32	
73	100	2.6					72	78	87	+9		Pat ent died	
74	100	2.8											

\*Watson test

†After three weeks

‡After two weeks

The prothrombin level remained below normal after treatment in 35 cases. Twenty-five were cases of chronic hepatitis, and 1 was a case of common-duct stone with biliary cirrhosis. In 5 cases of acute hepatitis, 3 patients died, and 2 made slow recoveries. There was 1 case of cancer of the liver, 3 of obstructive jaundice due to cancer of

TABLE 2. Number of Cases with Abnormal Tests before and after Treatment.

DIAGNOSIS	No. of Cases	HIPPURIC ACID EXCRETION		PROTHROMBIN LEVEL	
		BEFORE	AFTER	BEFORE	AFTER
Chronic hepatitis	54	45	40	27	25
Acute hepatitis	16	15	10	12	5
Obstruction	14	13	11	9	3
Tumors and so forth	11	6	8	3	1
Gall bladder disease	5	2	2	2	1
	100	83*	71	53	35

\*In 8 cases, no oral hippuric acid test could be performed.

the head of the pancreas, and 1 of cholecystitis, with postoperative bronchopneumonia and abscess of the lung.

### Diagnosis

Table 1 shows all the cases in which the initial prothrombin level was below normal. The initial prothrombin values and those found after three or four days of treatment with vitamin K are given, as well as the net change in the prothrombin level during that period. The initial prothrombin level was similar in the three groups,—obstructive jaundice, acute hepatitis and chronic hepatitis,—but the response to treatment with vitamin K was very different.

In the obstructive cases, the initial prothrombin level was below normal in 8 of 14 cases and, as a rule, rose quickly to normal in one to three days. In the cases of acute hepatitis, the prothrombin level rose rapidly to normal in the majority of cases, possibly because the tests were made at the time recovery began. In 2 fatal cases (Cases 14 and 88), the prothrombin level fell. In 1 (Case 17), the prothrombin fell at first and slowly returned to normal. In 1 (Case 87) of acute liver necrosis due to carbon tetrachloride poisoning, the prothrombin gradually rose to normal, but the patient died later of septicemia with metastatic abscesses.

The 27 cases of chronic hepatitis with an initial low prothrombin level behaved quite differently from those in the other two groups. After treatment, there was a well-marked rise in only 2 or 3 cases; in 13, there was a slight rise; in 5, there was no change; and in 6, 4 of which were fatal, the level fell. In most of these cases, the prothrombin remained at a distinctly low level of about 40 to 50 per cent after vitamin K therapy, which is quite un-

like the first two groups, in which the level rose to normal except in a small percentage of cases (Table 1).

### Correlation of Visible Bleeding with Prothrombin Levels

In the whole group, there were 6 cases of visible bleeding associated with low prothrombin levels (5, 20, 23, 27, 30 and 35 per cent): 1 case of bleeding from the nose and gums, 2 of ecchymosis, 1 of hematuria, 1 of hematuria and bleeding from the nose and gums, and 1 of hemoptysis. Pohle and Stewart<sup>10</sup> found 10 such cases (7 per cent) among 136 cases of liver and biliary-tract disease.

It is interesting to note that there were 15 other cases with low prothrombin levels (10, 15, 16, 23, 24, 27, 28, 29, 29, 30, 30, 30, 31, 32 and 35 per cent) and no visible bleeding. Pohle and Stewart found 15 such cases (11 per cent) in their group of 136 cases.

There were 8 other cases of bleeding with normal prothrombin levels; 4 cases of gross hematemesis, 1 of melena that was probably due to varices in cirrhosis, 2 of epistaxis, and 1 of melena with cancer of the rectum.

### COMMENT

*Methods.* The variation in methods for performing the hippuric acid excretion test by the gravimetric method may account for the different normal values cited by various authors. Our experience and that of Snell and McGith<sup>21</sup> and of Quick<sup>15</sup> show that the greatest number of normal tests with the method used have ranged between 2.5 and 3.5 gm., with occasional values at 4 and 5 gm. When hippuric acid crystals in the urine are subjected to the additional procedure of salting out, as suggested by Weichselbaum and Probst<sup>22</sup> and later by Quick,<sup>23</sup> the majority of normal values fall in the higher range.

A confusing factor in prothrombin determination is due to the fact that some workers use the initial prothrombin percentage and others the response to vitamin K analogues. The latter seems to be the better criterion, since the variable factor of adequate vitamin K is ruled out. Moreover, the initial figures do not have any possible differential value.

After performing a large number of prothrombin tests and correlating them with clinical observations, we considered a value of 80 to 100 per cent to be within normal limits. When the time of the unknown was shorter than the normal control, the value was recorded as 100 per cent.

Acetone extracts of whole rabbit brain, even in dilution, gave no constant value that could be du-

plicated and therefore were considered unsatisfactory.

Blood collected for this determination should not be allowed to stand for more than four hours, because fibrinogen is precipitated and is a definite source of error.

The curve shown in the paper by Kark and Lozner<sup>16</sup> was used in converting coagulation time to prothrombin per cent.

Dilution of the plasma for the prothrombin test may be a source of error.

**Correlation of tests.** It is obvious that the degree of correlation between the two tests is very poor, and that the prothrombin test does not discover the milder grades of liver damage but only those that are well marked. The prothrombin level was abnormal in only 53 per cent of the cases; it may be normal when liver damage is well marked and readily shown by other tests. This agrees with the work of DeLor and Reinhart<sup>24</sup> and of Lucia and Aggeler.<sup>14</sup>

**Prognosis.** The prognostic value of an increased prothrombin level after treatment is definite but limited in scope. In diseases of the liver after adequate treatment with vitamin K, several types of response occur. The prothrombin level may return to normal within twenty-four to forty-eight hours in some patients, or may rise gradually over a period of weeks. In other cases, it may fail to rise or may actually fall despite adequate therapy. In cases in which after vitamin K treatment the prothrombin level rises only a little, fails to rise or falls, the prognosis is progressively poorer. A falling prothrombin level with adequate vitamin K therapy usually means irreversible damage to the liver and corresponds quite well with low hippuric acid test values. All 4 patients in whom this occurred died within a short time.

On the other hand, in the cases in which the prothrombin percentage returns to normal, the test is a much less accurate guide in prognosis than the hippuric acid excretion, since the prothrombin level may become normal or approximately normal in the presence of serious disease of the liver. Four patients—2 with cancer of the liver, 1 with cancer of the pancreas, and 1 with acute hepatitis with multiple abscesses—died within a week after normal prothrombin determination. The hippuric acid test was very low in all. This is entirely in agreement with Quick's<sup>25</sup> recent statement that good liver function and a low prothrombin level are better from the patient's point of view than poor liver function and a high prothrombin level.

In estimating the risk at operation in diseases of the liver and biliary passages, the prothrombin

level is the best guide to the presence of a bleeding tendency, but the hippuric acid excretion has proved much better than the prothrombin percentage in revealing general hepatic insufficiency.

In cirrhosis, the prothrombin level may not respond well to treatment, but the percentage of normal prothrombin can be kept well above the bleeding level. Bleeding in the hepatic cirrhoses

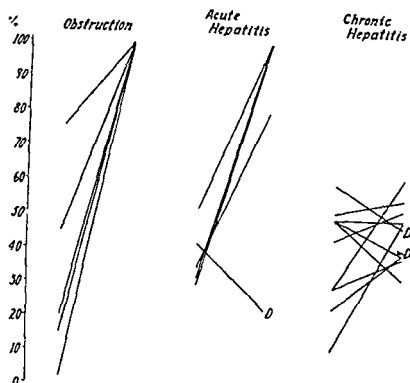


FIGURE 1. Early Prothrombin Response to Vitamin K Treatment in 20 Cases.

was about as often due to ruptured varices as to a low prothrombin level in our experience.

In one patient with cirrhosis, the prothrombin percentage remained low after injections of naphthoquinone derivatives, and a poor prognosis was given, but proved to be an error. When this patient was seen a year later, after much restriction in the use of alcohol and a more normal diet, the prothrombin level was found to be 100 per cent of normal, but the hippuric acid and brom-sulfalein excretion was definitely diminished.

In short, in response to vitamin K treatment in the patient with a relatively good liver function (early obstruction), or with a recovering liver (acute hepatitis), the prothrombin level returned rapidly to normal; with severe chronic damage (chronic hepatitis), the prothrombin level remained relatively low.

A small number of cases of acute hepatitis with low initial prothrombin percentage showed rapid increase to normal, after the use of increased amounts of glucose and fluids and without the aid of vitamin K analogues. It has been suggested that glucose plays a vital role in blood coagulation.<sup>26</sup>

**Fatal cases.** The prothrombin levels were low a few days to a week before death, in spite of ac-

tive treatment with vitamin K, in 7 cases with an acute element: 2 of acute hepatitis (prothrombin levels of 10 per cent), 4 of acute exacerbations in chronic hepatitis, and 1 of cholecystitis with an acute lung abscess (32, 40, 48, 48 and 53 per cent, respectively).

The prothrombin levels were low in 4 other cases tested one to two months before death: 2 of cardiac cirrhosis and 2 of portal cirrhosis (23, 33, 28 and 42 per cent, respectively).

The levels were high or normal within a week of death in 4 cases: 3 of cancer of the liver and 1 of cancer of the pancreas (70, 80, 98 and 100 respectively).

The levels were also high in 6 cases tested one month before death: 3 of cirrhosis, 1 of pylephlebitis and 2 of cancer of the liver (81, 90, 90, 95, 100 and 100, respectively).

In contrast to these results, the hippuric acid was always low or very low in fatal cases tested within a week of death (0.3, 0.3, 0.4, 0.7, 1.2, 1.3, 1.7 and 2.0 gm.), and was low in every fatal case but one (cardiac cirrhosis) tested one to two months before death (0.3, 0.4, 1.5, 1.7 and 2.0 gm.).

*Diagnosis.* The prothrombin level has some suggestive value in differential diagnosis of diseases of the liver, but the results must be interpreted with some degree of caution. One feature stands out: a prompt return to normal after vitamin K treatment has been found more commonly in obstructive jaundice than in some types of parenchymal damage, but a sharp distinction must be made between acute and chronic forms of the latter.

Andrus<sup>12</sup> has emphasized the value of prothrombin tests in the study of liver function. He states:

The [prothrombin] test finds one of its greatest fields of usefulness in distinguishing between jaundice of extrahepatic origin due, for example, to obstruction of the common duct by tumor or stone and that due to parenchymal liver disease. In brief, we have found that in the former, the plasma prothrombin either remains above 80 per cent or if it be depressed, rises following the intramuscular injection of 2-methyl-1, 4-naphthoquinone by more than 10 per cent in the first forty-eight to seventy-two hours. In intrahepatic jaundice the prothrombin, which here is uniformly depressed, either fails to rise by this amount or continues to fall.

In 40 jaundiced patients,—25 with common-duct obstruction and 15 with parenchymatous liver disease,—he found the test to be almost 100 per cent correct.

An effort was made to use this rapid type of response to vitamin K treatment as an aid in the diagnosis of obstructive jaundice. In 4 cases of

severe jaundice with acholic stools for a period of one or two weeks, in which the diagnosis of obstruction was seriously considered, there was an immediate rise to normal in the prothrombin level on vitamin K therapy; however, all these cases were proved to be acute parenchymatous hepatitis by an unmistakable course and subsequent history.

In our 14 cases of obstructive jaundice, there were 9 (64 per cent) with low initial prothrombin levels. The percentage of such cases has been higher in other reported series—Stewart and Rourke<sup>9</sup> found 80 per cent in 24 cases, and Pohle and Stewart<sup>27</sup> 87 per cent in 23 cases.

The presence or absence of urobilinogen in the urine and feces has proved to be the most valuable differential test between completely obstructive and parenchymatous jaundice. The hippuric acid and bromsulfalein tests have no differential diagnostic value, since they are positive in nearly every case of liver disease, regardless of its type.

#### SUMMARY

The blood prothrombin level and its response to vitamin K treatment were compared with standard liver-function tests, such as the hippuric acid and fractional bromsulfalein excretion, and the urobilinogen in the urine in a group of 100 cases of various diseases of the liver, and although of prime value in revealing vitamin K deficiency, was found to be of secondary importance as a liver-function test.

The degree of correlation between the prothrombin level and the liver-function tests used was very poor. The prothrombin test does not reveal the milder grades of liver damage but only those that are well marked. It was abnormal in only 53 per cent of the cases, and may be normal when liver damage is well marked and easily shown by the other tests.

The prothrombin level was less definite in prognosis than the liver-function tests used (with the single exception of discovery of a bleeding tendency). If normal, it may be misleading. An abnormal test is significant, and if a low prothrombin level rises but little, fails to rise or falls after vitamin K treatment, the prognosis is progressively unfavorable. In acute hepatitis, a falling prothrombin level in the presence of adequate vitamin K usually means irreversible, widespread liver damage.

In differential diagnosis of diseases of the liver the prothrombin level has only a suggestive and limited value. The sole diagnostic point noted is that the prothrombin percentage is much likelier to rise rapidly to normal after vitamin K treatment

in obstructive jaundice and healing acute hepatitis than in chronic hepatitis (cirrhotoses).

In some cases of acute hepatitis with low initial prothrombin levels, there has been a rapid response to active glucose and fluid intake comparable to that in similar cases treated with vitamin K.

Bleeding in the hepatic cirrhotoses was about as frequently due to ruptured varices as to a low prothrombin level.

The authors acknowledge their indebtedness to Dr Robert Kark, formerly research fellow in medicine, Harvard Medical School, for prothrombin data in some of the earlier cases, and to Miss Dorothy Jensen and Mr. William Appleby for technical assistance.

## REFERENCES

- Quick, A. J., Stanley Brown, M., and Bancroft, F. W. A study of the coagulation defect in hemophilia and in jaundice. *Am J M Sc* 190 501-511, 1935.
- Smith, H. P., Warner, E. D., and Brinkhaus, K. M. Prothrombin deficiency and the bleeding tendency in liver injury (chloroform intoxication). *J Exper Med* 66 801-811, 1937.
- Warren, R., and Rhoads, J. E. The hepatic origin of the plasma prothrombin observations after total hepatectomy in the dog. *Am J M Sc* 198 193-197, 1939.
- Quick, A. J. Nature of the bleeding in jaundice. *J A M A* 110 1658-1662, 1938.
- Butt, H. R., Snell, A. M., and Osterberg, A. E. The preoperative and postoperative administration of vitamin K to patients having jaundice. *J A M A* 113 383-390, 1939.
- Warner, E. D. Discussion of Butt, Snell and Osterberg.\*
- Kark, R., and Souter, A. W. Synthetic vitamin K in treatment of hypoprothrombinemia. *Lancet* 111149-1153, 1940.
- Wilson, S. J. Quantitative prothrombin and hippuric acid determinations as sensitive reflectors of liver damage in humans. *Proc Soc Exper Biol & Med* 41 559-561, 1939.
- Stewart, J. D., and Rourke, G. M. Control of prothrombin deficiency in obstructive jaundice by use of vitamin K. *J A M A* 113 2223-2227, 1939. Prothrombin and vitamin K therapy. *New Eng J Med* 221 403-407, 1939.
- Pohle, F. J., and Stewart, J. K. Observations on the plasma prothrombin and the effects of vitamin K in patients with liver or biliary tract disease. *J Clin Investigation* 19 365-372, 1940.
- Smith, H. P., Jiffen, S. E., Owen, C. A., and Hoffman, G. R. Clinical and experimental studies on vitamin K. *J. A. M. A.* 113-380-383, 1939.
- Andrus, W. DeW. The newer knowledge of vitamin K. *Bull New York Acad Med* 17-116-134 1941.
- Kark, R., White, F. W., Souter, A. W., and Deutsch, E. Blood prothrombin levels and hippuric acid excretion liver function test in liver disease. *Proc Soc Exper Biol & Med* 46 424-426, 1941.
- Lucas, S. P., and Aggeler, P. M. The influence of liver damage on the plasma prothrombin concentration and the response to vitamin K. *Am J M Sc* 201 326-340 1941.
- Quick, A. J. The synthesis of hippuric acid: a new test of liver function. *Am J M Sc* 185 630-635, 1933.
- Kark, R., and Lerner, E. L. Nutritional deficiency of vitamin K in man: a study of four non-jaundiced patients with dietary deficiency. *Lancet* 21167, 1939.
- Wallace, G. B., and Diamond, J. S. The significance of urobilinogen in the urine as a test for liver function with a description of a simple quantitative method for its estimation. *Arch Int. Med* 35 698-725, 1925.
- Deutsch, E. A fractional bromosulfalein test to determine residual liver damage in the nonjaundiced patient. *New Eng J Med* 225 171-175, 1941.
- White, F. W. The galactose tolerance and urobilinogen tests in the differential diagnosis of painless jaundice. *Am J Digest Dis & Nutrition* 4 315-325, 1937.
- White, F. W., Deutsch, E., and Maddock, S. The comparative value of serum hippuric acid excretion, total cholesterol, cholesterol ester, and phospholipid tests in diseases of the liver. I. The results of the tests. *Am J Digest Dis* 6 603-610, 1939. II. A clinical comparison of the tests. *Ibid.* 7 37 1940.
- Snell, A. M., and McGath, T. B. The use and interpretation of tests in the urine as a test for liver function. *J A M A* 110 167-174, 1938.
- Weichelsbaum, T. G., and Probst, J. G. Determination of hippuric acid in urine. *J Lab & Clin Med* 24 636-639 1939.
- Quick, A. J. Clinical application of hippuric acid and prothrombin tests. *Am J Clin Path* 10-222, 1940.
- DeLor, C. J., and Reinhart, H. L. An analysis of the hippuric acid, galactose tolerance, bromsulphalein and prothrombin tests in 381 cases. *Am J Clin Path* 11 617-622, 1940.
- Quick, A. J. Discussion of Sharp, E. A. Vitamin K activity of 2-methyl-L, 4-naphthoquinone. *J A M A* 114 439, 1940.
- Tocantins, L. M., and O'Neill, J. F. Increased plasma prothrombin activity after epinephrine injections, relation to hyperglycemia. *Proc Soc Exper Biol & Med* 47:477-479 1941.
- Pohle, F. J., and Stewart, J. K. The cephalin cholesterol flocculation test as an aid in the diagnosis of hepatic disorders. *J Clin. Invest.* 20:241-247, 1941.

## FRACTURES AROUND THE ANKLE JOINT\*

WILLIAM DARRACH, M.D.†

NEW YORK CITY

ANY pain or interference with the function of the ankle joint is a real handicap, whether the patient is a longshoreman, a clerical worker or a playboy. Injuries to this part of the body can be handled more intelligently and more successfully if the details of anatomy, physiology and pathology are understood and the general principles applied in each case than if a fixed rule of procedure is followed blindly.

### Anatomy

The lower extremity of the tibia expands and becomes four sided. Its medial portion projects down as the medial malleolus. Articulating with the outer side is the expanded lower end of the fibula, which forms the lateral malleolus. The lower surface of the tibia is concave and articu-

lates with the upper surface of the talus, which is narrower behind than in front and is in close contact on either side with the articular surface of the malleoli. The lower tibia and the two malleoli are spoken of as the mortise of the ankle, the talus being the tenon. The stability of the ankle, and indeed of the whole foot and leg, depends a good deal on the strength and accurate fitting of this tenon and mortise. It allows free flexion and extension, but no lateral motion; inversion and eversion of the foot take place in the subtalar and midtarsal joints. These three bones are held firmly in place by strong ligaments, which are also essential to stability. In front of and behind the adjacent margins of the lower tibiofibular joint are strong transverse bands, the anterior and posterior lower tibiofibular ligaments. In addition, and of vital importance, is the interosseous ligament. These three structures hold the lower ends of the tibia and fibula together and prevent a spreading

\*Presented at the New England Postgraduate Assembly, Cambridge, Massachusetts, November 13, 1940.

†Professor of clinical surgery, Columbia University College of Physicians and Surgeons, attending surgeon, Fracture Service, Presbyterian Hospital, New York City.



of the mortise. The anterior and posterior tibio-talar ligaments are rather weak and of minor significance. The medial collateral ligament is a broad band passing from the under aspect of the medial malleolus forward, downward and backward in a fan-shaped manner, to be attached to the medial aspect of the talus, sustentaculum tali and adjacent surfaces of the navicular. It is a continuous sheet. On the outer side, the lateral collateral ligament is made up of three separate, distinct bands. The medial passes from the tip of the fibula to the outer surface of the os calcis, the anterior goes forward and inward to the body of the talus, and the posterior, which is the strongest, passes almost horizontally inward to the outer tubercle of the talus.

#### *Mechanism of Injury*

When undue strain is brought to bear on the ankle, various things happen. The medial malleolus may give way near its tip or at the base, or the medial collateral ligament may tear. On the outer side, one may find a similar tear of the ligament or lower transverse or higher oblique breaks of the lateral malleolus, or the fibula may give way in its lower shaft. If the strain on the mortise is too great, the lower tibiofibular ligaments may give way or, rarely, tear off a portion of the adjacent tibia. When the force is against the lower surface of the tibia, the posterior or anterior lip may give way.

Considering the problem from the standpoint of the causative factor, one finds that if the foot is overinverted the lateral malleolus may be pulled off, or the medial one pushed off, or the lateral collateral ligament torn. If the foot is everted, the medial malleolus or medial collateral ligament may give way, or the lateral malleolus may be forced off. If the latter holds, the lower tibiofibular ligaments give way. Rotation of the foot on the leg is apt to tear off the medial malleolus, or to give a high spiral fracture of the fibula. With compression, a tibial lip or an extensive comminution of the whole lower tibia may result. When the foot is forcibly driven backward, the wider anterior part of the talus spreads the mortise, and the malleoli or the interosseous ligament gives way.

In a few cases, one of these five forces—inversion, eversion, compression, rotation and backward thrust—may act alone, but usually several act together, especially in the severer injuries. If one enumerates the various combinations of lesions encountered in this region, the list becomes quite alarming. The classification that is useful from a practical standpoint of teaching, treatment and prognosis includes four main groups, with three other less common but serious varieties.

#### *Types of Injury and Their Treatment*

The first group comprises cases of fracture of either malleolus, without displacement and without gross ligamentous injury. These require no reduction, but a brief period (several days) of immobilization and elevation. A posterior molded plaster splint, removed for application of heat, massage and active motion, gives comfort. Weight bearing, with support, is allowed after seven to ten days. Full use is permitted in three to five weeks.

The second group differs from the first only in that there is displacement of the foot, which requires reduction and slightly longer immobilization. In addition to the posterior splint, a sugar tong or bilateral molded splint, to control the inversion and eversion, is used. Weight bearing is allowed about the fourth week.

In both groups, some cases show distinct evidence of marked joint swelling, with a good deal of pain made worse by any movement of the ankle. Relief of this pain can be obtained by aspiration of the joint. Removal of even 4 or 5 cc. of bloody fluid gives marked relief; as much as 15 cc. has been obtained. This should be carried out only with strict precautions, a small nick in the skin being made with a pointed knife and the needle inserted through this rather than forced through the skin.

The third group includes fractures of either malleolus, with tear of the opposite collateral ligament, or bimalleolar fractures with lateral or medial displacement of the foot, but without injury to the tibiofibular ligaments. Reduction is necessary. The foot must be brought into position under the leg, and one must hold the malleoli in place by molding the plaster splint carefully against and beneath the malleoli until the plaster has hardened. It is better to have the splints pass above the flexed knee, to control rotation. They may be shortened after two weeks. Weight bearing, with protection, is started after four weeks.

In the fourth group,—the true Pott's fractures,—in addition to a fracture of the medial malleolus or a tear of the medial collateral ligament, there is a high fracture of the fibula and, most important of all, a disruption at the lower tibiofibular joint. This results in an outward and posterior displacement of the foot on the leg. A satisfactory result depends on a satisfactory apposition of the normal relation, which should be maintained until the various injured structures have healed sufficiently to withstand the strain put on them.

After a careful study of x-ray evidence to determine just what the lesion is, the knee is flexed under anesthesia, to relax the gastrocnemius and to afford countertraction against the thigh. Steady:

downward traction on the foot, the heel being held with one hand and the dorsum of the foot with the other, is gently and gradually applied with increasing force for several minutes. This usually overcomes the lateral displacement of the foot. The hand over the dorsum is then released and used to press backward on the tibia just above the ankle, forcing the foot forward on the leg. The thumb and fingers of the upper hand are used to approximate the malleoli, reducing the disruption of the lower tibiofibular joint. Splints are then applied by an assistant while the position is maintained by the operator, who shifts his hands in such a way as to maintain the traction and forward pressure of the foot, as well as the compression of the malleoli. This must be maintained until the plaster is sufficiently hard. With this type, it is necessary to maintain the immobilization for four to six weeks, although the knee can be mobilized at the end of two weeks. No weight bearing should be allowed for eight weeks, even with support. Disability lasts for three to four months or even longer.

Another type differs from the true Pott's fracture in that the fibula is not broken, but the main lesion is the disruption of the lower tibiofibular joint, with or without a fracture of the medial malleolus. This group is very important, because unless the diagnosis of disruption of the mortise is made and the treatment adjusted accordingly, the patient is very apt to have a permanent, marked disability. Unless firm union is obtained at this joint, the widened mortise leads to instability and persistent pain, which may last for years. If there is any doubt in the surgeon's mind, he should test the ankle under the fluoroscope to see if outward pressing of the foot tends to widen the mortise.

Another group includes cases of extensive comminution of the lower tibia, with any of the other lesions in addition. Accurate reduction can rarely be obtained by manipulation alone. Wire traction through the os calcis, with or without a second wire through the tibia above, sometimes accomplishes a fair reduction, but this type usually belongs in the operative class.

Another type is not a separate group, but includes fractures of either the posterior or the anterior lip of the tibia. The former is by far the commoner injury, and may be found as a complicating factor in any of the groups mentioned above.

Frequent failure to obtain or maintain satisfactory position in complicated ankle fractures, prolonged disability and the frequency of permanent disability have in recent years led me to put more of the severe types of ankle injuries into the oper-

ative class. By means of accurate, internal fixation, it has been possible to dispense with prolonged immobilization by splints and to start active motion a few days after the accident. I now believe that practically every disrupted lower tibiofibular joint should be operated on, and the two bones held in firm approximation by means of a transfixing bolt. In cases complicated by an anterior or posterior lip of the tibia or in comminuted cases, fragments can be realigned and held in position by screws, and small plates have frequently been used on the fibula. The results of this method have been most encouraging, and the disability time has been very markedly decreased.

As in any form of internal fixation of fractures, special technic, instruments and team training are essential, but if treatment is carried out with care, I believe that a great deal of time can be saved and permanent disability avoided.

The walking plaster boot is being used more and more. Certain precautions are indicated. This boot should be employed only when an accurate reduction has been obtained and maintained. It should be applied only after the primary swelling has subsided. Since the dependent position tends to increase congestion and swelling, the patient should be instructed to put his leg up at frequent intervals during the day. Sufficient cotton or sponge rubber should be placed between the sole of the foot and the plaster to lessen pressure. The boot must fit snugly beneath the expanding portion of the upper tibia. One disadvantage of this method is that it prevents the use of any heat, massage or active motions of the ankle. It is very useful, however, for patients who must be up and around for economic or other reasons.

\* \* \*

Fractures around the ankle joint frequently result in a good deal of permanent disability and pain. If the cases are seen early and an exact evaluation of the various lesions is made by careful examination and thorough study of clear x-ray films, excellent reductions can usually be obtained in the first few hours. The method of splinting, the time of immobilization and the question of weight bearing should be determined by the probable length of time required for solid healing of the most serious lesion.

Widening of the mortise due either to disruption of the lower tibiofibular joint or to imperfect reduction is a most disabling affair. Disruption of the mortise can easily be overlooked, and should be searched for in each case. The operative treatment of the more complicated cases, in proper hands, will shorten the period of disability and improve the end results.

180 Fort Washington Avenue

## HEREDITARY TELANGIECTASIS

## Report of a Case

LAWRENCE I. STELLAR, M.D.\*

BOSTON

**H**EREDITARY telangiectasis is a pathologic condition that occurs in and is transmitted through both sexes. The characteristic lesions—small red or purplish papules—occur in the mucous membranes, especially those of the upper respiratory and gastrointestinal tracts, in the skin and in some viscera. The papules consist of vessels made up of a single layer of endothelial cells and an abnormally thin epithelium. These vessels have a tendency to rupture, and thus give rise to bleeding. Hemorrhage has been reported most commonly in the form of epistaxis but, of course, may be seen elsewhere. The amount of blood loss tends to increase in later life.

The criteria for the diagnosis of this condition have been established by Goldstein<sup>1</sup> and affirmed by Larrabee and Littman<sup>2</sup> as follows: definite heredity, visible telangiectases, with pathologic distribution, and a tendency to bleed from the lesions.

According to Goldstein,<sup>1</sup> at the end of 1930, case reports of this condition involved about 550 members of 90 to 95 families. In spite of its rarity, hereditary telangiectasis should be thought of in the presence of bleeding; otherwise, the correct diagnosis may be missed or delayed. In the following case, the diagnosis was missed at each admission to the hospital.

## CASE REPORT

C. G., a 56-year-old Canadian-born housewife, had been admitted several times to the Boston City Hospital.

From puberty on, she experienced recurrent nosebleeds preceding her menstrual periods. In 1928, she began to have severe nasal bleeding two or three times daily. Occasionally, the bleeding stopped for as long as 2 weeks and then recurred. The blood usually came from both nostrils, and sometimes amounted to a "large wash-basin full."

From time to time, there were "pins-and-needles" sensations in the fingertips. The tongue became sore, and there was some nausea, and generalized weakness. Because of increasing dyspnea, orthopnea and occasional precordial pain on exertion, the patient was unable to walk more than a few feet.

In 1933, she entered the hospital for the first time because of these symptoms. She remained for 2 months, during which she was given a transfusion and iron and ammonium citrate. Three small hemorrhages occurred

from the nose during this admission. Because of home problems, the patient was discharged, with no complaints except fatigue.

After discharge, she continued taking iron quite regularly for about a year and thereafter intermittently. She soon began to suffer again from nosebleeds, mostly from the left side, occurring one to three times weekly. She remained fairly well, however, until 1936, when she developed symptoms similar to those complained of on the first admission—in addition to bouts of vomiting, feverishness, night sweats and some ankle edema.

Eight months later, the patient entered the hospital again. The treatment consisted of transfusions, iron and daily intramuscular injections of liver extract. The patient was discharged in 5 weeks feeling quite well.

From this time on, although the patient at each hospital entry showed marked anemia, the source of blood loss was obscure. In 3 years, during which she took iron intermittently, she had three admissions to the hospital. Her complaints were similar to those noted on the first two admissions, but except for occasional streaks of blood after blowing her nose, no history of gross epistaxis could be obtained. The only other source of blood loss was infrequent bleeding from hemorrhoids. The patient denied tarry stools. Treatment each time was essentially similar to that noted on the last admission and was always effective.

In 1917, after a "blood test," the patient was given intravenous and intramuscular medication for several years. Then, she was told that her "blood was negative." In 1918, she had "rheumatic arthritis" for a few months. She apparently required no bed rest. In 1937, she was told that she had "rheumatic heart disease." Because of her economic situation, her diet had always been rather low in meat.

The hospital records showed that her mother had severe nosebleeds, anemia and telangiectases of the lips, tongue and fingers; an autopsy report at another hospital noted "severe anemia and multiple bleeding points in the gastric mucosa." The patient stated that her grandmother, great-aunt and great-grandmother supposedly died of "bleeding diseases." She had one daughter, who had had no history of bleeding or telangiectasia.

Physical examination showed a well-developed, middle-aged woman, who was orthopneic, dyspneic and pale. On the anterior portion of the tongue, especially, there were several small, round, bright-red papules, 2 to 3 mm. in diameter (Fig. 1). In addition, telangiectases were noted on the left cheek, the mucocutaneous junction of the upper lip, the right conjunctiva, and all over the nasopharynx.

During the patient's first admission, nose and throat consultants found scales in both nares, but no bleeding. At the last entry, a few small telangiectatic spots were seen on the anterior septum and also on the lateral nasal walls. At the mucocutaneous junction of the left naris were two small telangiectatic areas. The left anterior septum showed a large superficial ulcer of the mucosa. The only actual point with crusted blood was over this ulcer. At

\*Formerly, house officer, Third Medical Service (Tufts), Boston City Hospital; resident, First Medical Service (Tufts), Boston City Hospital.

most entries there was clotted, red blood in the left nostril. The palate, the posterior pharynx and the roof of the nasopharynx also showed telangiectases. No attempt was made to treat these lesions, because none could be proved as the source of the bleeding.

The fundi were normal except at the first admission when each fundus showed a small red area suggestive of hemorrhage.

During several admissions, the cardiac findings varied. At one time, a high pitched, blowing systolic murmur was heard all over the precordium, the pulmonic second sound

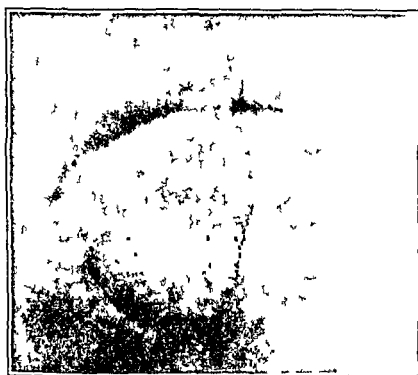


FIGURE 1 Photograph of Tongue of Patient C G Showing Telangiectases

was greater than the aortic, the heart was slightly enlarged to the left by percussion. On another occasion systolic and presystolic murmurs were heard at the apex. During the last admission, a Grade 2 systolic murmur was heard best in the 4th left interspace, 4 cm to the left of the midsternal line, and a few medium moist rales were present at the right base.

At the last entry, there was a slight tenderness in the right upper quadrant and the liver was felt three or four fingerbreadths below the costal margin. Previous to this admission, tenderness in the right upper quadrant was noted once the liver was questionably palpable another time, and definitely felt down to the umbilicus on another occasion. The spleen was not felt. At the last two admissions there was slight pitting edema of the feet. Rectal examination showed three or four anal tags and small hemorrhoids. The vaginal examination was negative.

On the several admissions the temperature varied from 98.8 to 100.2°F, the pulse from 88 to 124, and the respirations from 25 to 28.

The hemoglobin level and red cell count at the time of each entry and discharge are presented in Table I.

The white cell counts varied from 7400 to 19000. On the occasion when they were elevated they quickly fell to normal. On the first admission the mean corpuscular volume was 98 cubic microns, the mean corpuscular hemoglobin, 137 micromicrograms, and the mean corpuscular hemoglobin concentration 19.5 per cent. From 33 to 145 per cent reticulocytes were found, the latter occurring as a peak count following the administration of

iron. A typical smear showed 82 per cent polymorphonuclears, 15 per cent basophils, 1 per cent eosinophils, 6 per cent small lymphocytes, 2 per cent large lymphocytes, 7 per cent monocytes and 0.5 per cent myelocytes, there were occasional normoblasts, increased and large platelets, poikilocytosis and anisocytosis. One smear showed decreased platelets. The bleeding time was about 4 minutes, once, it was reported to be over 10 minutes. The clotting time was 5 to 8 minutes, on one occasion, it was noted that clot retraction was poor. The tourniquet test was negative, and the prothrombin time was normal. The red blood cells hemolyzed in solutions containing 0.44 to 0.36 per cent sodium chloride.

The cholesterol was 84 mg, the uric acid 47 mg, the nonprotein nitrogen 22 mg, the calcium 88 mg, and the

TABLE I Hemoglobin Levels and Red Cell Counts at Each Admission

ADMISSION	DATE	HEMOGLOBIN LEVEL %	RED CELL COUNT $\times 10^6$
First	1/25/33	8	0.9
	3/7/33	30	7.3
Second	9/14/33	9	1.8
	10/21/37	75	4.4
Third	6/23/38	10	0.9
	7/23/38	64	3.1
Fourth	1/9/39	18 gm	1.2
	1/26/39	64 gm	2.0
Fifth	9/23/40	10	1.2
	11/5/40	56	2.8

phosphorus 37 mg per 100 cc. The phosphatase was 4.3 Bodansky units, and the icteric index 2. The blood was Type IV (Moss); the blood Hinton reaction was negative, and the formal gel test was negative.

The urine showed a specific gravity of 1.008 to 1.011, a negative test for albumin and a few white blood cells per high power field in the sediment. The specific gravity on each sample of urine obtained was in this range. No concentration tests were done.

No stools were studied at the first admission; on the second admission one stool gave a +++ guaiac reaction, on the third admission, many stools gave up to ++++ guaiac reactions and were still strongly positive on discharge; at the fourth admission one stool was benzidine negative and on the fifth admission many stools gave + to ++++ guaiac reactions and were strongly positive on discharge.

Typical electrocardiogram showed a sinus bradycardia and rather low voltage.

Gastric analyses on four occasions showed no free hydrochloric acid even after histamine. On the first analysis no guaiac test was recorded. The other three were done during the last admission and the tube was passed through the mouth on each occasion. One was guaiac negative and the other two showed gross fresh blood.

Two barium enemas showed incomplete filling of the cecum; a third examination 6 months later was completely negative.

Three gastrointestinal series were negative. The last was done with follow-through studies because of the barium enema results first obtained.

Sigmoidoscopy showed a normal pale mucosa.

Following final discharge the patient was observed for 6 months. The hemoglobin level and red cell count climbed slowly to 65 per cent and 3,500,000, respectively, although the stools showed a persistent ++ to +++ guaiac reaction.

## DISCUSSION

In most cases of hereditary telangiectasis, the hemoglobin very rarely falls to such low levels as those recorded in this case. Houser<sup>3</sup> states that the mortality from hemorrhage is 4 per cent. In most of the cases in the literature, the hemoglobin was noted to be from 50 to 60 per cent.

The patient's diet, which had not been completely adequate, could not explain the picture of anemia without obvious bleeding. During the first two admissions, the source of the blood loss was obvious. In subsequent admissions, the nose could not be incriminated, except for the possibility of postnasal drip, of which the patient was unaware. This was never observed during the last admission, even though she was examined before arising from the horizontal position in the morning.

The only obvious bleeding point in the later hospital entries was a superficial ulcer on the septum. This showed clotted blood on several admissions. The aural consultants did not consider this lesion sufficient to cause the marked anemia. O'Kane<sup>4</sup> reported a case with a ++++ guaiac reaction in the stool that cleared only on treatment of the nasal telangiectases with a sclerosing solution. In his case, the hemoglobin was 50 per cent, and the red-cell count was 3,100,000.

This patient presented the problem of a possible primary lesion in the gastrointestinal tract, as suggested by the first barium enemas. She had a large liver on several entries; this was noted definitely for the first time, three years before the last entry. During the last admission, the liver did not shrink more than 1 cm. as the cardiac failure was relieved. No nodularity of the liver was observed. A final gastrointestinal series and another barium enema six months later did not reveal a cecal lesion. The patient's good and repeated response to treatment and the failure to lose weight also militate against the view that a primary cecal lesion might have been responsible for the melena.

Boston<sup>5</sup> and Goldstein<sup>1</sup> presented cases of gastric hemorrhages due to telangiectases. In the case reported above, two gastric analyses during the last admission showed fresh blood, although the samples were removed through the mouth; however, a properly handled Levin tube does not usually give fresh blood. The mother's autopsy showed "bleeding points" in the gastric mucosa. Gastrointestinal telangiectases must be strongly considered in both the patient and her mother.

Fitz-Hugh<sup>6</sup> has drawn attention to a marked intolerance to blood transfusion, resulting in severe jaundice, in patients with Type IV blood and splenomegaly and hepatomegaly. This patient was Type IV and presented hepatomegaly, but no splenomegaly. She had eight transfusions. Three moderate chills, one with vomiting, were the only reactions recorded.

One final interesting fact has been noted by several observers—namely, the disappearance of some lesions and the appearance of others. Apparent fundic lesions described in the first admissions have since disappeared.

## SUMMARY

A case of hereditary telangiectasis that fulfilled the criteria for diagnosis is presented. The patient showed a very marked anemia on repeated occasions, at first because of nasal hemorrhage, later possibly as a result of gastrointestinal bleeding. The possibility of a separate pathologic lesion in these cases must be kept in mind, but this seems to be ruled out in the case under discussion.

## REFERENCES

1. Goldstein, H. I. I. Goldstein's hereditary angiomatosis with recurring familial hemorrhages (Rendu-Osler-Weber's disease). *Arch. Int. Med.* 48:836-865, 1931. Hereditary multiple telangiectasia. *Arch. Dermat. & Syph.* 26:282-308, 1932.
2. Larrabee, R. C., and Littman, D. Hereditary hemorrhagic telangiectasia: with a report of five cases in two families. *New Eng. J. Med.* 207:1177-1182, 1932.
3. Houser, K. M. Hereditary hemorrhagic telangiectasia. *Ann. Otol., Rhin. & Laryng.* 43:731-738, 1934.
4. O'Kane, G. H. Hereditary multiple telangiectasis with epistaxis. *J. A. M. A.* 111:242-244, 1938.
5. Boston, L. N. Gastric hemorrhage due to familial telangiectasis. *Am. J. M. Sc.* 180:798-802, 1930.
6. Fitz-Hugh, T., Jr. Splenomegaly and hepatic enlargement in hereditary hemorrhagic telangiectasia. *Am. J. M. Sc.* 181:261-268, 1931.

## MEDICAL PROGRESS

HEMATOLOGY: ANEMIA, WITH PARTICULAR REFERENCE TO  
THE HEMOLYTIC SYNDROME\*

WILLIAM DAMESHEK, M.D.†

BOSTON

**A**NEMIA is but a symptom and is therefore always secondary to some other disorder, and so-called "primary" anemia is a thing of the past. Modern classifications of anemia stress cell size and the color index. Thus, anemias are either macrocytic, normocytic and microcytic or hyperchromic, normochromic and hypochromic. These classifications are very useful, since macrocytic, hyperchromic anemias are often deficient in "liver-extract" or vitamin B complex; normocytic, normochromic anemias often indicate that the bone marrow itself is involved by hypoplasia, aplasia, sclerosis, leukemia or metastatic cancer, whereas microcytic hypochromic anemias usually mean that red-cell formation is normal but that hemoglobin is either lacking (iron-deficiency anemia) or cannot be properly synthesized.

## HYPOCHROMIC MICROCYTIC ANEMIAS

A deficiency in iron for the available red-cell formation in both the bone marrow and the blood results either from continued blood loss or from such abnormalities as an inadequate intake of iron in the food, achlorhydria, malabsorption from the bowel and multiple pregnancies. Usually, multiple etiologic factors are necessary before a well-defined anemia results. The condition often known as idiopathic or primary hypochromic anemia, which is usually described in middle-aged women, is also the end result of numerous factors, the most important of which is perhaps the complete histamine achlorhydria. That this condition may be a forerunner of pernicious anemia has been stated a number of times. Miller and Dameshek<sup>1</sup> report 2 cases of primary hypochromic anemia that terminated as pernicious anemia. The first case showed "sideropenic dysphagia," generally known as the Plummer-Vinson syndrome, and developed pernicious anemia a number of years after a typical hemoglobin deficiency had been found. The second case appeared to be a typical case of chronic iron deficiency until iron was

given, following which the features of pernicious anemia became apparent. These cases are of some theoretical interest, since they indicate that the gastric mucosa may first be incompletely atrophic, leading to a disturbance in the digestion of iron-containing foods, and later completely atrophic, resulting in such great diminution in the secretion of Castle's enzyme that the liver-extract deficiency state known as pernicious anemia results. It is probable, as Miller and Dameshek pointed out, that the gastric disturbance starts early in life and, if sufficiently marked in adolescence and early adulthood, may result in the development of the iron-deficiency anemia known as "chlorosis." This condition is by no means extinct, as both Alsted<sup>2</sup> and Olef<sup>3</sup> have shown. Although Olef attempts a clear-cut discrimination between chlorosis and the so-called "primary hypochromic anemia," such a differentiation is probably to be questioned, since the cases merge into one another and, except for age, are really identical in underlying physiology, objective signs and response to therapy. Chlorosis is in all probability idiopathic hypochromic anemia in a somewhat younger age group than most of the cases. When the latter are analyzed, however, a history of long-standing anemia extending back fifteen to thirty years is usually obtained. This illustrates again the value of analyzing the life history of a disease rather than of interpreting it from a single snapshot.

Work on the absorption and metabolism of iron by means of radioactive iron continues in several laboratories.<sup>4</sup> Ross and Chapin<sup>5</sup> found that the greatest absorption took place in patients with chronic hypochromic (presumably, iron-deficiency) anemia. By this method, cases of pernicious anemia were found to have an iron deficiency that became apparent only after the erythrocyte response to liver extract had occurred. Fowler and Barer,<sup>6</sup> who studied this problem without recourse to the radioactive technic, suggested that iron had, in addition to its action as replacement therapy, a stimulating effect on hemoglobin formation. In another investigation, the same authors<sup>7</sup> discovered that the addition of copper sulfate to the iron preparation (ferric ammonium citrate) used did not

Reprints of articles in this series are not available for distribution, but the articles will be published in book form. The current volume is *Medical Progress Annual, 1940* (Springfield, Illinois: Charles C. Thomas Company, 1941. \$1.00).

\*From the Joseph H. Pratt Diagnostic Hospital, and the Blood Clinic of the Boston Dispensary.

†Visiting physician and consulting hematologist, Joseph H. Pratt Diagnostic Hospital; chief, Blood Clinic, Boston Dispensary.

increase the effectiveness of iron in the hemoglobin regeneration of mild hypochromic anemia in the adult.

### HYPERCHROMIC MACROCYTIC ANEMIAS

#### *Pernicious Anemia*

Despite minor modifications, Castle's theory regarding the interaction of intrinsic factor derived from the stomach and extrinsic factor derived from the food continues to stand firm. Very careful and elaborate observations by Formijne<sup>8</sup> demonstrated again that liver extract was not formed by the interaction of extrinsic and intrinsic factor in vitro, and could be produced only in vivo. A series of carefully controlled observations in swine—in which total gastrectomy was performed, the animals killed at various intervals, and the livers assayed for potency by testing in human cases of pernicious anemia—is reported by Geiger, Goodman and Claiborn.<sup>9</sup> Following total gastrectomy, the liver gradually became depleted of antianemic potency; this indicates that it serves either as a storage reservoir or as an elaborating and storing center. By other ingenious experiments, it was confirmed that gastric digestion was essential for the production of the erythrocyte-maturation factor, although it was also shown (as Meulengracht had previously indicated) that the duodenum is a significant source of intrinsic factor. Despite removal of the entire stomach and the duodenum, with great reduction in the antianemic potency of the swine's liver, it was, however, impossible to produce in these animals the typical human blood picture of pernicious anemia. Ivy<sup>10</sup> and Wintrobe and his co-workers<sup>11</sup> have also failed to produce the blood picture of pernicious anemia either by gastrectomy in various animals or by the use of a diet grossly deficient in various factors of the vitamin B complex. Wintrobe et al. were, however, able to produce neurologic phenomena closely resembling those found in pernicious anemia by a diet deficient in pantothenic acid, pyridoxin and choline. Whether these studies have any definite relation to pernicious anemia remains to be seen.

The long-standing question regarding the relation of the fish tapeworm (*Diphyllobothrium latum*) and pernicious anemia is still under discussion. Von Bonsdorff<sup>12</sup> reports 14 typical cases of pernicious anemia in carriers of the worm. In the first 9 cases, treatment with an anthelmintic filicin was followed by a distinct reticulocyte response and a complete remission; liver extract was not used. Reticulocytosis began directly after expulsion of the worm. In 1 case, liver extract was necessary for a complete remission. In the last 4 cases, the worm cure had little or no effect on the anemia, which was completely relieved by

liver extract. In these cases, there was apparently only a coincidental relation between the simultaneous presence of the worm and the severe anemia. Von Bonsdorff believes that in many cases the tapeworm interferes with the absorption of the liver-extract substance from the bowel, and that although the anemia can be cured with liver extract, removal of the worm is of fundamental importance.

Jones<sup>13</sup> and Meyer, Schwartz and Weissman<sup>14</sup> discuss the problem of gastrectomy and the anemias. Jones states, "It is apparent that major gastric surgery may be performed without any great fear of undue consequences as far as the factor of normal hematopoiesis is concerned . . . [although] an occasional severe microcytic or macrocytic anemia may ensue . . . many months following operation." Meyer and his co-workers report such a case, which five years after complete gastrectomy developed pernicious anemia. The value of long-continued observation of patients who have undergone extensive gastric operations is stressed.

Although pernicious anemia in the Negro is usually considered extremely rare, McCracken<sup>15</sup> reports 3 cases and states that the incidence of the disease in the Negro is 1 per 100,000, as compared with 35 per 100,000 in the white race. Schwartz,<sup>16</sup> who has observed a large number of cases of pernicious anemia in Negroes at the Cook County Hospital, Chicago, stresses the diagnostic difficulties in some of the cases, which may masquerade as a subacute or chronic infectious process.

Treatment of the disease has been quite well standardized in this country, since the various products have been assayed and labeled according to their unit potency. Such assays must still be performed in previously untreated human cases, because no satisfactory animal method has been found. Worth watching, however, is the method of Crandall, Finne, and Smith,<sup>17</sup> which utilizes dogs with internal bile fistulas (anastomosis of the gall bladder to the right renal pelvis, with ligation of the common bile duct). A hyperchromic, macrocytic anemia, apparently responding to liver extract, gradually follows this operation. Jacobson and Subbarow<sup>18</sup> report on recent advances in the purification of active substances from liver extract. Although the primary factor has still not been obtained in crystalline form and several factors are probably required to give the full effect, these investigators report that recent refinements in preparation have resulted in the development of a material that is highly effective in an average dosage of only 7 mg. every ten days.

Askey,<sup>19</sup> arguing that the liver in a case of pernicious anemia is completely lacking in specific

substance, suggests the use of a single massive dose of liver extract (150 to 400 U.S.P. units) given intramuscularly without other treatment. Clinical and hematologic responses were excellent and well maintained in the majority of the cases for several months. A massive initial dose to "stock the liver," followed by monthly doses to maintain adequate storage, appeared sufficient to give optimum results in most cases. This method of therapy cannot be recommended. It is not known how much of the massive dose is quickly excreted in the urine; stocking the liver is not the essential thing; curing the liver-extract deficiency throughout the body is essential, and the most physiologic method possible should be used. For this reason, regular doses—preferably every week or two—are far preferable, although still not entirely physiologic. Evans and Jordan<sup>20</sup> found that a highly concentrated liver-extract preparation in 1-cc. doses parenterally was more effective both hematologically and neurologically than the cruder preparations. Neural symptoms and signs were controlled or actually improved in the great majority of cases. Zillhardt, MacLean and Murphy<sup>21</sup> found that the combination of thiamin (vitamin B<sub>1</sub>) and parenteral liver extract "might have a beneficial effect on those residual neural signs and symptoms of pernicious anemia that seemed stationary in spite of persistent, intensive anti-pernicious anemia therapy." The authors rightly advise caution in the interpretation of their results. No effects were obtained when the vitamin was given orally, or when vitamin B complex (containing thiamin) was given parenterally.

#### HEMOLYTIC SYNDROMES

Interest in the numerous hemolytic syndromes continues to run unusually high. They may be classified as follows:

- A. Hemoglobinurias (exceedingly rapid hemolysis, with hemoglobinemia and hemoglobinuria)
  1. Paroxysmal cold
  2. Paroxysmal nocturnal
  3. March
  4. Favism
  5. Unclassified types
- B. Hemolytic anemias
  1. Hereditary
    - a. Spherocytic
    - b. Target-cell (Mediterranean)
    - c. Sick-cell (African)
  2. Acquired (acute, subacute and chronic types)
    - a. Chemical, including the sulfonamide drugs
    - b. Immune body (hemolysins and agglutinins), including erythroblastosis foetalis
    - c. Idiopathic, including hypersplenic types
    - d. Symptomatic

Although this classification seems to offer some help, it is realized that it probably has only transitory significance. It is somewhat unorthodox in that hereditary (usually called "congenital") hemolytic jaundice or anemia, which is generally considered to be spherocytic, is subdivided into spherocytic, target-cell and sickle-cell types; it will be noted, furthermore, that erythroblastosis foetalis is included under the acquired hemolytic processes in association with the presence of immune bodies.

#### Mechanisms

Much discussion continues to center about the etiologic mechanisms relating to the hemolytic syndromes. In some, as in paroxysmal cold hemoglobinuria, these have been rather well worked out; in others, they are as obscure as ever. It should be realized that increased blood destruction may be due to numerous causes and that multiple mechanisms are often present. A theory that attempts to explain all the hemolytic syndromes on the basis of a single mechanism must on occasion be stretched rather fine. Theories at present being discussed are as follows:

*Hereditary defect of "erythron."* This is accepted by most authors as the cause for congenital spherocytic hemolytic jaundice, and perhaps also for the target-cell and sickle-cell types. Unless they are caused by some definite etiologic agent, many acquired cases with spherocytosis are even said by extreme protagonists of this view to be due to a congenital defect of the red cells, latent for many years.

*Stasis.* The chief protagonists of this theory are Ham and Castle,<sup>22</sup> who point out that stasis results in increased spheroidicity of the red cell and, ultimately, in its hemolysis. Hemolytic reactions are thought to be due to extreme stasis, especially in the spleen, or to agglutinative reactions. This theory does not explain, among other conditions, march hemoglobinuria or the hemolytic syndromes associated with actual hemolysins.

*Hemolysins.* Dameshek and Schwartz<sup>23</sup> found hemolysins in the blood in certain cases of acute hemolytic anemia, and by the injection of immune hemolysins they were able to reproduce spherocytosis and various types of hemolytic syndromes.<sup>24</sup> They contended that hemolysins might be at the bottom of many of the hemolytic syndromes, including congenital spherocytosis. If by "hemolysin" is meant an agent—chemical, immune-body or cellular—that causes injury to red cells, this idea may be well taken, although the hemolysis of simple stasis, unusual exertion and so forth is not explained. Although Ham and Castle prefer to designate the hemolysis following agglutination



as a phenomenon of stasis, Dameshek and Miller<sup>25</sup> have shown that agglutination causes injury to the red-cell envelope, with the result that it becomes readily vulnerable to mechanical trauma, stasis and the effects of complement activity.

*Lysolecithin.* Bergenhem and Fahraeus<sup>26</sup> demonstrated that normal blood serum contains a lytic substance, which they called "lysolecithin." They demonstrated that it became increased with stasis and concluded that it was responsible for normal blood destruction in the chief organ of stasis—the spleen. They suggested that hemolytic anemias might simply be due to an increased concentration of lysolecithin acting on the erythrocytes passing slowly through the spleen. Singer<sup>27</sup> described a method for the extraction of lysolecithin from the serum and for quantitative measurement of its hemolytic power. He also described the lysolecithin fragility test, apparently specific for the spherocytes of congenital hemolytic jaundice. In a later paper, Singer<sup>28</sup> pointed out that "the significance of lysolecithin as the physiological hemolysin involved in the mechanism of normal blood destruction . . . is not conclusive," and that it was not likely that lysolecithin could be regarded as responsible for the increased blood destruction in congenital hemolytic jaundice, especially since no increase in the production of this lysin was demonstrable in the disease. Singer concluded that lysolecithin, although it had hemolytic qualities, was not the hemolysin causing hemolytic anemia.

*Spleen.* Because of the dramatic effects of splenectomy in many cases of hemolytic anemia, of both the congenital and acquired types, the spleen has naturally been singled out as the chief offender by most observers. What the spleen actually does still remains a mystery. According to Ham and Castle,<sup>22</sup> it acts like a test tube, allowing normal red cells to stagnate and become somewhat spheroidal and causing the abnormal spherocyte to become hemolyzed. According to Bergenhem and Fahraeus,<sup>26</sup> lysolecithin and the spleen are closely related. Dameshek and his co-workers<sup>24, 29</sup> assume that the spleen is the chief organ of hemolysin production, and other observers, notably Doan,<sup>30</sup> arrive at a somewhat similar conclusion by stating that blood destruction has to do with the reticuloendothelial system, of which the spleen is the largest factor. That some cases of hemolytic anemias are solely hypersplenic cannot be denied; in others, the spleen seems to be secondarily enlarged, and splenectomy may or may not be of value. Direct observation of the living spleen in the rat by means of transilluminated quartz rod was first performed by Knisely,<sup>31</sup> and on the basis of his work, it seemed clear that

circulation in the spleen is of the closed variety and that blood often stagnates there, perhaps for hours. However, in a more recent communication, MacKenzie, Whipple and Wintersteiner,<sup>32</sup> using a modification of the same technic, came to diametrically different conclusions—that is, that the spleen possessed an open circulation and that the pulp spaces, not the venous sinuses, were the primary physiologic units of the splenic vascular mechanism. Studies of the spleen in experimentally produced hemolytic anemia revealed that spherocytes were trapped outside sinusoids and then presumably became hemolyzed. Singer, Miller and Dameshek<sup>29</sup> studied subjects splenectomized for various causes and found that blood destruction, as measured by the fecal urobilinogen output, became greatly reduced; this might be associated with the fact that a thinner, more resistant cell population, together with increased numbers of target cells, was present. The spleen was found to have other functions, which are described below. From all these studies, it may safely be concluded that the exact relation of the spleen to hemolytic anemia is not yet clear, nor can one say with any degree of assurance which of the various theories described above fits most closely the pattern of the observed facts.

### *Hemoglobinurias*

*Paroxysmal nocturnal hemoglobinuria.* This disorder, which has been studied extensively by Ham<sup>33</sup> and by Ham and Dingle,<sup>34</sup> is associated with an increase in the acid fragility of the red cells. The fundamental cause of the disorder remains obscure, although there is some evidence that the red cells are injured by an immune body (hemolysin?) since complement results in hemolysis. Ham and Horack<sup>35</sup> made the interesting observation that certain cases of chronic hemolytic anemia may not show the characteristic nocturnal episodes of hemoglobinuria except at infrequent intervals. The acid fragility test of Ham thus becomes an important diagnostic test in atypical hemolytic syndromes, especially when splenectomy is being considered, since removal of the spleen is without therapeutic effect in paroxysmal nocturnal hemoglobinuria.

*March hemoglobinuria.* Gilligan and her collaborators<sup>36, 37</sup> have made careful studies of the interesting condition known as march hemoglobinuria. In this curious condition, first described in soldiers, "black water" develops with specific types of exercise, such as strenuous marching and running. Hemoglobinuria does not develop when the patient assumes a kyphotic instead of a lordotic position while exercising. Gilligan et al. studied the

renal threshold for hemoglobin in the blood plasma, its quantitative excretion in the urine, the spectrophotometric analysis of the pigment and various possible pathogenetic mechanisms. No clues regarding the etiology of the condition were found, although much useful information concerning the pathologic physiology of the hemoglobinurias was obtained.

**Favism.** Luisada<sup>38</sup> has contributed a comprehensive article on favism, which he considers "a singular disease chiefly affecting the red blood cells." This condition, which is chiefly restricted to the inhabitants of Sardinia, results either from the ingestion of the fava bean or from inhalation of its flowers, and is characterized by the sudden appearance of hemoglobinuria, jaundice and vascular symptoms. Luisada believes that the condition represents an anaphylactic reaction in which the red cells are directly injured.

**Other hemoglobinurias.** Altschule and Gilligan<sup>39</sup> report a case of acute, massive hemoglobinuria in an old man without demonstrable cause and bearing, apparently, little relation to the other types of hemoglobinuria. This study is distinguished chiefly by the careful measurements of the various metabolic changes in blood pigment, and by the discussion of the differential diagnosis of hemoglobinuria. Calculations of the amount of hemoglobin lost during the attack, as computed by various methods, showed that approximately 1400 cc. of blood was hemolyzed during the first week, 400 cc. during the second week, and 200 cc. during the third. In another paper, Gilligan and Kapnick<sup>40</sup> reported hemoglobinuria occurring during treatment with sulfanilamide. It is recommended that, in addition to transfusions, sodium bicarbonate be added in sufficient quantity to keep the urine alkaline. This is said to protect the kidneys against damage caused by deposition of hemoglobin pigment in the tubules.

### *Hereditary Hemolytic Anemias*

**Spherocytosis.** Lloyd<sup>41</sup> has contributed a significant (unfortunately not very accessible) monograph on the etiology of "acholuric family jaundice," in which the various abnormalities in the disease are assessed according to the theories discussed above. Singer's<sup>28</sup> finding that the spherocytes of this disease are abnormally fragile to lysolecithin is confirmed, and Lloyd also agrees with Singer that there is not enough evidence to incriminate lysolecithin. Some very ingenious experiments are recorded in which exsanguination was performed on a newborn monster and transfusions were given (on separate occasions) from 2 persons with congenital hemolytic spherocytic

jaundice, one of whom had been splenectomized, the other being an active case. The recipient lived long enough for observations to be made. Whereas the red cells of the splenectomized patient became rapidly more spherocytic and were quickly destroyed in the circulation of the monster (who possessed a normal spleen), the red cells of the active spherocytic case became no more spherocytic than in their own circulation. From these observations, the author concludes:

The pathological blood destruction of the disease is dependent upon the inheritance of an abnormality of the erythron. As the result of this defect the red cells are abnormally susceptible to damage in their passage through the spleen by a process which, very probably, causes little or no permanent damage to the normal erythrocyte. . . . It is possible that lysolecithin . . . will cause permanent damage to the red cells of acholuric family jaundice, indicated by spherocytosis which persists until the death of the cell, but which is not sufficient to cause permanent alteration in the normal erythrocyte.

These in vivo experiments result in conclusions similar to the in vitro findings of Ham and Castle,<sup>22</sup> but they still do not explain the "why" of the congenital spherocytosis, which may be the result of the activity of an inherited hemolytic factor on the non-nucleated erythrocyte. Nor is the abnormally diminished blood destruction following splenectomy in this congenital type of hemolytic jaundice explained<sup>42</sup>—that is, although spherocytosis is still present, blood destruction is less than normal, indicating that the spherocyte has a normal resistance within the circulation and that the spleen has an active (hemolytic?) effect in destroying erythrocytes. This is also indirectly brought out in the report of a series of 3 cases of hemolytic crisis occurring in 3 members of one family with hereditary spherocytic jaundice.<sup>42</sup> That all these persons developed very severe anemia, necessitating emergency splenectomy within a few days of each other, makes it possible that the cause of the suddenly enhanced spherocytosis was outside the marrow and perhaps splenic in origin.

Dameshek and Singer<sup>43</sup> direct attention to a type of familial jaundice without bile in the urine and nonhemolytic in type (familial nonhemolytic jaundice). This condition, in which persistent although somewhat variable and usually mild jaundice is present, may be confused either with familial hemolytic jaundice or with mild hepatic disease. It is distinguished from the former by the normal size, thickness and fragility of the red cells, by the lack of reticulocytosis and by the absence of all evidence of increased blood breakdown, particularly in the fecal urobilinogen out-

put. It is distinguished from hepatic disease by the long course, its familial nature and the complete normality of the liver-function tests. As demonstrated by the bilirubin-excretion test, the condition is apparently due to a delayed excretion of indirect bilirubin from the blood stream by the liver cells, with resultant retention. The liver itself is histologically normal, as recently shown by Krarup and Roholm.<sup>44</sup> A very careful evaluation of the bilirubin-excretion test is that of Weech, Vann and Grillo.<sup>45</sup>

*Target-cell anemia.* Under this designation, I<sup>46</sup> described the case of an Italian youth who showed marked hypochromic anemia, jaundice, marked splenomegaly, generalized osteoporotic changes and the presence of many target cells in the blood. These cells, which look like a target or bull's eye in stained preparations, are abnormally thin and unusually resistant to hypotonic saline solutions. Because this patient presented most of the features of Cooley's anemia, and because cases of this Mediterranean disease show not only nucleated red cells but target cells and increased hypotonic resistance in the blood, the possibility was broached that the fundamental defect in both conditions was the target cell. Wintrobe, Matthews, Pollack and Dobyns,<sup>47</sup> reporting a similar condition in 14 members of three Italian families, stated that both Cooley's anemia and this milder Mediterranean condition represented an inherited defect—the production of unusually thin red cells. Other reports of what is probably the same condition are those of Strauss, Daland and Fox<sup>48</sup> and of Eliel and Bayles.<sup>49</sup> From further studies of these conditions,<sup>50</sup> it appears that familial target and oval syndromes are relatively common in Italian families, that they are inherited as a dominant characteristic, and that great variabilities occur in their severity. Thus, Cooley's anemia appears to be the severest form, and target-cell anemia the next, a number of milder forms ("hypochromic polycythemia," refractory hypochromic anemia and so forth) being known.

Bohrod<sup>51</sup> rightly points out that the target cell is commonly found in many, particularly hypochromic, anemias. Barrett<sup>52</sup> first noted that these cells were found in unusually large numbers in sickle-cell anemia, following splenectomy and in obstructive jaundice and steatorrhea. Singer, Miller and Dameshek<sup>53</sup> found them constantly in splenectomized patients and explained the increased hypotonic resistance of the red blood cells on this basis. Bohrod attacks the concept that the target cell represents a cell that is perhaps defective, and maintains that it is merely representative of increased blood regeneration secondary to blood de-

struction or blood loss. This view does not agree with the observations that, following splenectomy, blood destruction is conspicuously diminished and target cells become greatly increased, that, in the familial Mediterranean cases, target cells are frequently numerous without any evidence of increased blood destruction, that, following splenectomy in Cooley's anemia, large numbers of target cells appear or that these cells are absent from cases of congenital and acquired spherocytic jaundice in which blood destruction is greatly increased.

*Sickle-cell anemia.* Bauer<sup>53</sup> contributes a comprehensive article on sickle-cell disease, in which valuable considerations regarding pathogenesis and the generalized character of the condition are discussed. Anemia is only one consequence of the sickle-cell trait, and is much less serious than the circulatory stasis in the small blood vessels of the internal organs, which is perhaps the primary and most disastrous consequence of the disease. Such stasis may be enhanced by surgical procedures and may be the fundamental cause of the anemia. It is recommended that all Negro patients be routinely examined for the sickle-cell trait, since this condition may result in disorders mimicking rheumatic fever, rheumatic heart disease, polyarthritis, osteomyelitis, various infectious diseases, cerebral conditions, peptic ulcer, appendicitis and so forth. Sickle-cell anemia with unusual bone changes is reported by Danford, Marr and Elsey,<sup>54</sup> with central-nervous-system involvement by Hughes, Diggs and Gillespie<sup>55</sup> and by Skoog,<sup>56</sup> and with ulcers of the legs by Cummer and LaRocco.<sup>57</sup> The reason for the development of these ulcers is still obscure despite very careful studies. Methods for the determination of the sickle-cell trait are described by Diggs and Pettit<sup>58</sup> and by Sherman.<sup>59</sup> The moist stasis method—Scriver and Waugh<sup>60</sup>—is recommended by Diggs and Pettit. Sherman describes a method for differentiating the sickle-cell trait and sickle-cell anemia by injecting red cells kept free from outside air into a solution of saline formalin. Since the sickle-cell trait may have no clinical significance, it is essential to differentiate it and the actual sickle-cell anemia.

#### *Acquired Hemolytic Anemias*

Fox and Ottenberg<sup>61</sup> present a careful study of the acute hemolytic anemia resulting from the sulfonamide drugs. This may be so severe as to result in shock and even death; in fact, 6 of their 9 cases ended fatally. The fundamental mechanism of the blood destruction is still obscure, although it may be allergic or due to the formation of unusual oxidation products that are

allergic or hemolytic. Emerson, Ham and Castle<sup>62</sup> came to similar conclusions. Fox and Ottenberg found that twelve to forty-eight hours after onset of hemolysis, the serum contained three blood pigments: hemoglobin, methemoglobin and Fairley's new pigment—methemalbumin.

Farrar, Burnett and Steigman<sup>63</sup> report a case of acquired hemolytic anemia in which a serum isohemolysin was found, similar to that found in the cases of Dameshek and Schwartz.<sup>23</sup> Splenectomy was curative.

Recent experience with cases of acute and subacute acquired hemolytic anemia of idiopathic variety reveals that only occasionally are hemolysins demonstrable. Splenectomy, although usually curative, may not result in recovery, particularly if the operation has been postponed too long while numerous transfusions have been given. Under these circumstances, not only may new agglutinins or hemolysins be built up, but unusual myeloid metaplasia may develop in spleen or liver. Cases of this sort may then not respond to splenectomy. In such cases, one should determine whether greatly increased blood destruction is present and should be sure that no underlying cause, such as leukemia or Hodgkin's disease, is present; only a minimum number of transfusions (one to three) should be given before splenectomy is performed. Many cases in infants and young children are probably of a milder form (so-called "Lederer's anemia"), and these patients frequently, but by no means always, recover without splenectomy. Such a case is reported by Sterner.<sup>64</sup>

Levine, Katzin and Burnham<sup>65</sup> indicate that erythroblastosis foetalis—icterus gravis neonatorum—is acute hemolytic anemia of the newborn and is caused by isoimmunization of an Rh-mother by an Rh+ fetus. The resultant anti-Rh agglutinin may then penetrate the placental circulation and cause agglutination, with consequent hemolysis of the infant's red cells. It is extremely important in these cases to give blood from an Rh- donor—not the mother. If testing for the Rh factor cannot be done, extremely careful cross-matching by means of the Landsteiner test-tube technic should be performed, with the modification that incubation of the serum, red-cell suspension and saline mixture be carried out for at least thirty minutes. By proper transfusion technic in these cases, the mortality rate should be considerably reduced.

The possibility that some cases of acquired hemolytic jaundice are secondary to some underlying process such as leukemia, Hodgkin's disease, lymphosarcoma or dermoid cyst is suggested by

Singer and Dameshek.<sup>66</sup> In one remarkable case, in which splenectomy resulted in only a temporary response, the finding and removal of a dermoid cyst resulted in complete cure.

113 Bay State Road

## REFERENCES

- 1 Miller E. B., and Dameshek W. "Primary hypochromic anemia terminating in pernicious anemia: report of two cases." *Arch Int Med* 68:375-394 1941
- 2 Alsted G. "Chlorosis: Essential juvenile iron deficiency anemia." *Am J Clin Med* 5:201-211 1941
- 3 Oiet J. "Chlorosis." *New Eng J Med* 225:358-365 1941
- 4 Dameshek W. "Hemolytic anemia." *New Eng J Med* 224:729-741 1941
- 5 Ross J. F. and Chapin M. A. "The selective absorption of radioactive iron by normal and iron deficient human subjects." *J Clin Investigation* 20:437-441 1941
- 6 Towler W. M., and Barer A. P. "Some effects of iron on hemoglobin formation." *Am J M Sc* 201:642-651 1941
- 7 Idem. "Effect of copper and iron on hemoglobin regeneration." *J Lab Clin Med* 26:837-836 1941
- 8 Forman P. "Experiments on properties of extrinsic factor and on resection of Castle." *Arch Int Med* 66:1101-1214 1940
- 9 Geiger A. J., Goodman L. S. and Clibborn L. V. "Effects of gastrointestinal resections in swine on anti-anemia potency of liver with observations on nature and sources of materials effective in pernicious anemia." *Yale J Biol & Med* 13:259-2/8 1940
- 10 Ivy A. C. "Effects of gastrectomy in animals." *Am J Digest Dis* 7:500-501 1940
- 11 Wintrobe, M. W., Miller, J. L. Jr., and Lisco H. "Relation of diet to occurrence of ataxia and degeneration in nervous system of pigs." *Bull Johns Hopkins Hosp* 67:37-405 1940
- 12 von Bonsdorff B. "On reticulocyte response and course of remission after removal of worm in patients with Diphyllobothrium latum and pernicious anemia." *Diphyllobothrium latum and pernicious anemia*. IV. *Acta Med Scandinav* 105:516-539 1940
- 13 Jones C. M. "Problem of gastrectomy and the anemias." *Am J Digest Dis* 7:507-505 1940
- 14 Meyer, K. A., Schwartz S. O. and Weissman L. H. "Pernicious anemia following total gastrectomy." *Arch Surg* 42:18-24 1941
- 15 McCracken J. P. "Pernicious anemia in the Negro." *J M A Georgia* 30:49-54 1941
- 16 Schwartz S. O. "Personal communication."
- 17 Crane E. W., Jr., Fennel C. O., Jr., and Smith P. W. "Experimental anti-pernicious anemia factor deficiency in dogs." *Science* 93:549-551 1941
- 18 Jacobson B. M. and Subbarow Y. "Studies of principle in liver effective in pernicious anemia: recent advances in purification of active substances." *J M A* 116:367-374 1941
- 19 Askey J. M. "Quantitative treatment of pernicious anemia: response to intramuscular massive dose of liver extract in relapse." *J M A* 117:907-910 1941
- 20 Evans T. S. and Jordán R. H. "Concentrated liver extract in maintenance treatment of pernicious anemia." *Am J M Sc* 202:408-416 1941
- 21 Zillhardt J. C., MacLean K. and Murphy W. P. "Effect of thiamin on residual neural disturbances of treated pernicious anemia." *Am J Med* 15:33-37 1941
- 22 Ham T. H. and Castle W. B. "Studies on destruction of red blood cells: Relation of increased hypotonic fragility and of erythroblastosis to the mechanism of hemolysis in certain anemias." *Proc Am Philo Soc* 82:411-419 1940
- 23 Dameshek W. and Schwartz S. O. "The presence of hemolysins in acute hemolytic anemia." *New Eng J Med* 218:75-80 1938
- 24 Idem. "Hemolysins as the cause of clinical and experimental hemolytic anemias with particular reference to the nature of spherocytosis and increased fragility." *Am J M Sc* 196:769-792 1938
- 25 Dameshek, W., and Miller, L. B. "Unpublished data."
- 26 Bergel em, R., and Palcaeus R. "Über spontane Hämolysebildung im Blut unter besonderer Berücksichtigung der Physiologie der Milz." *Ztschr J d ges Exper Med* 97:525-538 1936
- 27 Singer K. "Lysolethrin fragility test." *Am J M Sc* 199:466-477, 1940
- 28 Idem. "Lysolethrin and hemolytic anemia: Significance of lysolethrin production in differentiation of circulating and stagnant blood." *J Clin Investigation* 20:153-160 1941
- 29 Singer K., Miller E. B. and Dameshek, W. "Hematologic changes following splenectomy in man, with particular reference to target cells, hemolytic index and lysolethrin." *Am J M Sc* 202:177-187, 1941
- 30 Doan C. A. "The reticulo endothelial system." In *A Symposium on the Blood and Blood Forming Organs*. 264 pp. Madison University of Wisconsin Press 1940. Pp 167-193.
- 31 Knisely M. H. "Spleen studies. I. Microscopic observations of circulatory system of living unanesthetized mammalian spleens." *Anat Rec* 67:23-50 1936
- 32 Idem. "Spleen studies. II. Microscopic observations of circulatory system of living traumatized spleens and of dying spleens." *Ibid* 65:131-148 1936
- 33 Mackenzie D. W., Jr., Whipple A. O., and Winterstein M. T. "Direct observations on circulation of blood in transilluminated mammalian spleen." *Proc Soc Exper Biol & Med* 44:139-142 1940
- 34 Ham T. H. "Studies on destruction of red blood cells. I. Chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria: investigation of mechanism of hemolysis with observations on five cases." *Arch Int Med* 64:1771-1780 1933

34. Ham, T. H., and Dingle, J. H. Studies on destruction of red blood cells. II. Chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria: certain immunological aspects of hemolytic mechanism with special reference to serum complement. *J. Clin. Investigation* 18:657-672, 1939.
35. Ham, G. C., and Horack, H. M. Chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria: report of case with only occasional hemoglobinuria and with complete autopsy. *Arch. Int. Med.* 67:735-745, 1941.
36. Gilligan, D. R., Altschule, M. D., and Katersky, E. M. Studies of hemoglobinemia and hemoglobinuria produced in man by intravenous injection of hemoglobin solutions. *J. Clin. Investigation* 21:177-187, 1941.
37. Gilligan, D. R., and Blumgart, H. L. March hemoglobinuria: studies of the clinical characteristics, blood metabolism and mechanism, with observations on three new cases, and review of literature. *Medicine* 20:341-395, 1941.
38. Luisada, A. Favism singular disease chiefly affecting red blood cells. *Medicine* 20:229-250, 1941.
39. Altschule, M. D., and Gilligan, D. R. Acute, massive hemoglobinuria of obscure cause, with jaundice and anemia. *Arch. Int. Med.* 68:957-978, 1941.
40. Gilligan, D. R., and Kapnick, I. Clinical and laboratory observations on hemoglobinuria occurring during sulfanilamide therapy. *New Eng. J. Med.* 224:801-804, 1941.
41. Lloyd, T. W. *On the Aetiology of Achromic Family Jaundice*. Oxford University Thesis, 1941. Privately printed.
42. Dameshek, W. Familial hemolytic crisis: report of three cases occurring within ten days. *New Eng. J. Med.* 224:52-56, 1941.
43. Dameshek, W., and Singer, K. Familial nonhemolytic jaundice: constitutional hepatic dysfunction with indirect van den Bergh reaction. *Arch. Int. Med.* 67:259-285, 1941.
44. Krarup, N. B., and Roholm, K. Histologic studies by means of liver biopsy in intermittent jaundice of young persons. *Ugeskr. f. læger.* 103:72-75, 1941.
45. Weech, A. A., Vann, D., and Grillo, R. A. Clearance of bilirubin from plasma. Measure of excreting power of liver. *J. Clin. Investigation* 20:323-332, 1941.
46. Dameshek, W. "Target cell" anemia. Anergic type of Cooley's erythroblastic anemia. *Am. J. M. Sc.* 200:445-454, 1940.
47. Wintrobe, M. M., Matthews, E., Pollack, R., and Dobyns, B. M. Familial hemopoietic disorder in Italian adolescents and adults resembling Mediterranean disease (thalassemia). *J. A. M. A.* 114:1530-1538, 1940.
48. Strauss, B. B., Dajind, G. A., and Fox, H. J. Familial microcytic anemia: observations of six cases of blood disorder in an Italian family. *Am. J. M. Sc.* 201:30-34, 1941.
49. Elhel, L. P., and Bayles, T. B. Microcytic, hypochromic anemia, associated with splenomegaly and refractory to treatment: report of a case. *New Eng. J. Med.* 225:134-136, 1941.
50. Dameshek, W. Unpublished data.
51. Bohrod, M. G. The significance of target cells in anemia. *Am. J. M. Sc.* 202:869-874, 1941.
52. Barrett, A. M. A special form of erythrocyte possessing increased resistance to hypotonic saline. *J. Path. & Bact.* 46:603-618, 1938.
53. Bruer, J. Sickle cell disease: pathogenic, clinical and therapeutic considerations. *Arch. Surg.* 41:1344-1362, 1940.
54. Danford, E. A., Marr, R., and Elsey, E. C. Sickle cell anemia, with unusual bone changes. *Am. J. Roentgenol.* 45:223-226, 1941.
55. Hughes, J. G., Diggs, L. W., and Gillespie, C. E. The involvement of the nervous system in sickle-cell anemia. *J. Pediat.* 17:186-189, 1940.
56. Skoog, A. L. Cerebral complications in sickle cell anemia. *Scand. M. J.* 33:714-721, 1940.
57. Cummer, C. L., and LaRocco, C. G. Ulcers of legs in sickle cell anemia. *Arch. Dermat. & Syph.* 42:1015-1039, 1940.
58. Diggs, L. W., and Pettit, V. D. Comparison of methods used in detection of sickle cell trait. *J. Lab. & Clin. Med.* 25:1166-1171, 1940.
59. Sherman, I. J. The sickling phenomenon, with special reference to the differentiation of sickle cell anemia from the sickle cell trait. *Bull. Johns Hopkins Hosp.* 67:309-324, 1940.
60. Scriver, T. B., and Waugh, T. R. Studies on a case of sickle cell anemia. *Am. J. Dis. Child.* 40:922, 1930.
61. Fox, C. L., Jr., and Ottenberg, R. Acute hemolytic anemia from sulfonamides. *J. Clin. Investigation* 20:593-602, 1941.
62. Emerson, C. P., Ham, T. H., and Castle, W. B. Hemolytic action of certain organic oxidants derived from sulfanilamide, phenylhydrazine and hydroquinone. *J. Clin. Investigation* 20:451, 1941.
63. Larrar, G. E., Jr., Burnett, W. E., and Steigman, A. J. Hemolytic anemia and hepatic degeneration cured by splenectomy. *Am. J. M. Sc.* 200:164-172, 1940.
64. Sterner, L. G. Ein Fall von akuter hämolytischer Anämie vom Ledererschen Typ. *Acta paediat.* 28:196-206, 1941.
65. Levine, P., Katzin, E. M., and Burnham, L. Isoimmunization in pregnancy: its possible bearing on etiology of erythroblastosis fetalis. *J. A. M. A.* 116:825-827, 1941.
66. Singer, K., and Dameshek, W. Symptomatic hemolytic anemia. *Arch. Int. Med.* 15:544-563, 1941.

**CASE RECORDS OF THE  
MASSACHUSETTS GENERAL HOSPITAL**ANTE-MORTEM AND POST-MORTEM RECORDS AS USED  
IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor***CASE 28091****PRESENTATION OF CASE**

A fifty-two-year-old Canadian architect was admitted to the hospital because of dyspnea of several months' duration, following a series of neuromuscular symptoms extending over a period of years, for which he had been seen in the hospital previously.

About ten years before this last entry, there was gradual onset of numbness and tingling in the hands and feet, *sensation remaining unimpaired*. About six years later, the patient began to have progressive difficulty in walking, and became unsteady on his feet. Four months after this, he was admitted to the hospital, when the pupils were irregular and unequal, and reacted to distance though not to light. There was slight drooping of the upper lids. The legs appeared small, but not definitely atrophied. Deep tendon reflexes could not be obtained in arms, knees or ankles. Vibration sense was absent in the malleoli. Physical examination was otherwise negative. The blood Hinton reaction was negative. The cerebrospinal fluid showed a total protein of 80 mg. per 100 cc., a gold-sol curve of 0012210000, a negative Wassermann reaction and negative microscopy and dynamics. Other laboratory studies were negative. After discharge from the hospital, the patient was given various forms of arsphenamine treatment, which was discontinued because of severe reactions. The symptoms remained stationary for a few months. A right-foot drop then developed, requiring the use of a cuff about the foot, wired to a cuff about the calf, as an aid in walking. The right arm and right leg gradually became increasingly atrophic.

Eleven months before the last admission, the patient experienced unusual dyspnea and prostration, in the course of a coryza lasting several days. A similar attack, lasting three days, occurred seven months later. The dyspnea appeared to be paroxysmal, and was unassociated with any disturbance of heart action. A physician prescribed coramine. The patient went to the White Mountains for a short vacation, and returned after a week, complaining that the slight change in altitude had brought on a return of the dyspnea, with a

dry cough. He had a rise in afternoon temperature to 99 or 100°F. His physician noted a distinct expiratory murmur over the middle of the right lung, posteriorly, without rales or areas of dullness. The blood pressure was 110 systolic, 90 diastolic. A roentgenogram of the chest showed old apical tuberculosis on the right, with apparently enlarged lymph nodes at the hilus. Ten days before entry, there was rapid progression of the attacks of dyspnea, and the patient began to lose strength. His cough continued to be unproductive. He had no chills, sweats or chest pain. The blood pressure was 90 systolic, 70 diastolic, at this time. On the advice of a consultant, he was readmitted to the hospital.

The patient's father died of tuberculosis at forty-six years of age. The patient himself, when fifteen years old, spent a year at rest because of a suspicion of tuberculosis. Subsequently, the patient had never been vigorous, although he was seldom sick in bed. He had lived for two years in the Philippine Islands. Exposure to syphilis was denied. Shortly before the onset of the respiratory symptoms, an employee with whom he had worked in close contact for years was diagnosed as tuberculous.

On admission, the patient appeared well developed and nourished but somewhat dehydrated. The lips, fingers and upper chest were cyanotic. The veins of the neck and upper extremities were distended. The lower extremities were pale and cool. The heart was slightly enlarged. The pulmonary second sound was moderately loud, and there was a fairly loud systolic murmur, heard best over the lower half of the heart and toward the apex. There was dullness, with bronchial breathing, over the upper sternum, and a few fine rales at each base. The liver edge was palpable four or five fingerbreadths below the costal margin. There was slight pitting edema over the sacrum, but not in the extremities. The neurologic status was not reviewed at this time.

The temperature was 99°F., and the pulse was 90 and weak but equal in each wrist. The respirations were 20, without cough or wheeze. The blood pressure was 80 systolic, 40 diastolic.

Examination of the blood showed a red-cell count of 4,780,000 with 13.6 gm. hemoglobin, and a white-cell count of 21,000 with 78 per cent polymorphonuclears, 9 per cent small lymphocytes, 12 per cent monocytes and 1 per cent eosinophils. The blood Hinton reaction was negative. The nonprotein nitrogen was 33 mg. per 100 cc.

Roentgenologic examination of the chest showed marked enlargement of the pulmonary vessels toward the hilus, but not distally, with weak pul-

sations. The lung fields showed mottled and linear areas of increased density. There was questionable dilatation of the right ventricle.

An electrocardiogram showed right-axis deviation. All complexes were inverted in Lead 4, with prominent P waves.

The patient continued dyspneic. He was given oxygen, and a phlebotomy of 300 cc. was performed, without appreciable effect. Death occurred from respiratory failure on the third hospital day.

#### DIFFERENTIAL DIAGNOSIS

DR. J. H. MEANS: This somewhat complicated story divides itself fairly well into two chapters, which I might consider to some degree separately. The history ten years previously and continuing down to four years previously, when the patient was in the hospital for study, was characterized by some paresthesias and later by the development of difficulty in walking, unsteadiness on the feet and irregular, unequal Argyll-Robertson pupils, with ptosis of both eyelids, absent tendon reflexes and absent vibration sense; I cannot reconcile this with anything but tabes, perhaps of a rather burnt-out sort. There is no evidence to point to a diagnosis of combined system disease and no suggestive blood picture, nor is the story typical of such disease. The Argyll-Robertson pupil is fairly pathognomonic. The irregularity may likewise be due to syphilis. The blood Hinton reaction was negative. That does not signify anything because it is often negative in long-standing tabes of an inactive sort. The protein was elevated, and the gold-sol curve was not very impressive, but it had a hump in the middle that would go with tabes satisfactorily, so that I cannot get away from that diagnosis, and I therefore make it without more discussion.

Later, however, there were neurologic findings that were not consistent with tabes. Motor phenomena came on after some arsenical treatment, to which the patient responded poorly. A right-foot drop developed, which required apparatus to permit him to walk, and he developed muscle atrophy in the right leg and also in the right arm. This distribution of atrophy in the right arm and leg sounds as though he had had a cerebral lesion, but since the rest of the picture was very much more like that of a peripheral neuritis I must confess that I am puzzled. However, I believe that the foot drop was almost certainly due to peripheral neuritis. Of course, the reflexes were absent anyway because of tabes. I do not know what would happen to reflexes in the event that a tabetic patient, with no reflexes,

developed hemiplegia from a cerebral accident. What would happen?

DR. CHARLES S. KUBIK: The reflexes would remain absent.

DR. MEANS: Then we cannot say that this patient did not have some cerebral lesion, but I think it is most unlikely, and we have no proof. What I think he had was an arsenical neuritis, which gave him foot drop. Why the right arm rather than the left or some other part was also involved, I cannot say. It may have been just chance. At any rate, I am unable to go any farther with the neurologic diagnosis. I leave it there.

The symptoms in the second period, which began eleven months before entry, instead of pointing to the nervous system, involve the circulatory system in a somewhat puzzling fashion. Certain features about the symptomatology suggest an upper mediastinal pressure syndrome. We are told that the neck veins were dilated and that a venipuncture was performed in the hope of giving relief, and we are also told that the patient was cyanotic in his upper extremities, the upper chest, neck and face, but nowhere else. These manifestations go with an upper mediastinal pressure syndrome, and I dare say that the dyspnea might also be consistent. But other things do not fit that interpretation so well. There is some evidence of edema and congestive failure with a large liver, and perhaps an upper mediastinal pressure syndrome is not the most likely explanation.

Let us consider the various symptoms. As I read the second chapter, I was impressed with the following symptoms. In the first place, the paroxysmal dyspnea was unassociated with disturbance of the heart action. I am interested in the story that, after getting better, the patient became worse when he went to a somewhat higher altitude; this suggests that a relative oxygen want played a part in the dyspnea. The progressive fall in blood pressure may be significant—at any rate, it is very striking. It started as 110 systolic, 90 diastolic, and dropped to 80 systolic, 40 diastolic, shortly before he died. I am also impressed with the fact that there was some evidence of infection: a temperature of 100°F. and a leukocytosis that requires explanation. I am interested that there was evidence of old tuberculosis, with apical and lymph-node involvement. I am rather impressed with the progression of the attacks of dyspnea and the evident marked loss of strength.

The matter of tuberculosis might be discussed for a moment at this point. The patient had been suspected of having it in childhood. He

showed obsolete tuberculosis by x ray study. The exposure to the person with whom he worked in close contact does not impress me as being significant, because it is unlikely that one would catch tuberculosis at his age—he was beyond the age when one contracts new tuberculosis. He had been working with this person for years, however, but we do not know how many. I fancy he had tuberculosis before he established this contact, so that it is not of great importance.

It is to be observed that the patient denied exposure to syphilis, but I believe that he had had it. I do not see how we can escape that conclusion.

When he came into the hospital, the significant signs were the high venous pressure, the loud pulmonic second sound and the loud systolic murmur, heard best over the lower half of the heart and toward the apex. It did not go out to the axilla, like a mitral murmur, and seems to have been more in the region of the pulmonary area. He also had dullness, with bronchial breathing, over the sternum. Dullness there suggests dilatation of the great vessels or a mediastinal mass, or something of that kind that would go with the upper mediastinal pressure syndrome. There may have been some element of upper mediastinal pressure in addition to another factor that produced the rest of the picture. Later, the patient had a palpable liver and pitting edema, and the blood pressure dropped. The laboratory work, except for the leukocytosis and perhaps a monocytosis, does not help us much. The right axis deviation is of interest. The x ray examination described—I have not seen the films—some changes in the pulmonary vessels and some enlargement of the heart in the region of the right ventricle.

May we see the x-ray films and try to pull all this together?

DR. AUDREY O. HAMPTON: At the first examination, one might on first inspection call these enlarged lymph nodes at the lung roots, particularly since the patient had evidence of old tuberculosis, but in this Bucky film one can see that they are blood vessels. The blood vessels of the lung roots are grossly enlarged, and they end rather abruptly in the middle of the lungs.

DR. MEANS: Can you tell whether they are arteries or veins?

DR. HAMPTON: They are probably pulmonary arteries.

The film also shows a few rather short linear scars in the lungs scattered around in queer places below the site of the old tuberculosis; these scars were not present at the examination a month before.

DR. MEANS: Did the patient have emphysema?

DR. HAMPTON: The diaphragm is relatively low, but there was no note of limitation in excursion.

DR. MEANS: What about the upper mediastinum? Is there a mass of any kind?

DR. HAMPTON: No; the trachea is in normal position, and the main bronchi are normal.

DR. MEANS: Is there any stenosis?

DR. HAMPTON: No. This film shows a definite change in the bases of the lungs, as compared with those taken at the examination a month before. It looks like pulmonary edema, in addition to poorly outlined areas of consolidation.

DR. MEANS: Are these areas of fibrosis?

DR. HAMPTON: I think that this upper shadow is fibrous because of old tuberculosis, the remainder does not appear to be. There are no blebs. The heart is definitely enlarged. The supposition that the enlargement was right ventricular is, however, based on fluoroscopy.

DR. MEANS: Is there any reason to give up that idea?

DR. HAMPTON: None at all.

DR. MEANS: It seems to me that the high venous pressure, the cyanosis, the right-sided enlargement, the electrocardiogram showing right-axis deviation, and the engorgement of the pulmonary arteries by x ray studies, indicating high arterial pressure in the pulmonary artery, all fit the interpretation of this case as one of chronic cor pulmonale. The upper mediastinal pressure syndrome I should be inclined to give up because we have not found, by x ray or other examination, evidence of anything that could produce upper mediastinal pressure. Why only the upper half of the body was cyanotic, I cannot explain. Frankly, that puzzles me a good deal.

Why did the patient have cor pulmonale, and did he have anything else? I should like to throw in, not as a diagnosis but just by way of discussion, an idea that occurred to me as I went over this history. One of the conspicuous symptoms was paroxysmal dyspnea. One usually finds paroxysmal dyspnea in hypertension. This man was hypotensive. He had these paroxysms of dyspnea, and I do not believe that they were asthmatic because there is nothing to go with that. The low blood pressure, the prostration and the paroxysms of dyspnea are very impressive, and they make me think of an adrenocortical insufficiency, particularly since the last came on at a time when the patient did not have other cardiac symptoms, and I remember being told by one of my teachers that he had seen very striking paroxysms of dyspnea in Addison's disease. I looked through several textbooks of medicine and could



find nothing whatever about it. The Addisonian crises that are somewhat like shock are described, but nothing is said about paroxysmal dyspnea. I therefore called my teacher on the telephone,—it was Dr. William H. Smith,—and he said, "You are entirely correct; I have seen Addison's disease with symptoms of severe attacks of paroxysmal dyspnea." He said that Dr. George Sears had also seen it and had told him about it. I cite them as authorities that in Addison's disease one does get paroxysmal dyspnea. I am not prepared to say that this patient had Addison's disease, but I shall be interested in what is found in the adrenal glands, and if anything is found there pathologically I shall be satisfied; if it is not, I shall not be disappointed, because it is a long shot.

How can we put these findings together on one etiology? The tabes was due to syphilis, of course. Could the rest of it have been due to syphilis? Well, it could. Cor pulmonale occurs in Ayerza's disease, which is a type of syphilitic endarteritis of the pulmonary vessels. That is a possible explanation. It is also stated in the textbooks that sometimes syphilis affects both adrenal glands and produces adrenocortical insufficiency or Addison's disease, so that syphilis probably could explain everything except the peripheral neuritis, which is explained by the antisiphilitic treatment. However, we know that the patient also had tuberculosis,—we have evidence by x-ray examination and by the history,—and that he had been running a fever; the high white-cell count could have been due to active tuberculosis. Dr. Paul D. White,\* in his book, does not mention tuberculosis as a primary cause of cor pulmonale, but he does mention fibrosis. I suppose that tuberculosis produces fibrosis of the lungs; it certainly causes fibroid phthisis. This patient apparently did not have a serious enough process to cause cor pulmonale, but this is definitely a recognized possibility. Dr. White also mentions pneumoconiosis and silicosis as giving rise to fibrosis, which could produce cor pulmonale. I do not know that this man had any such exposure, so that I do not know which etiology is most likely here. We can explain everything on one etiology if we say this was syphilis, but on the doctrine of chances it is somewhat more likely to be on a tuberculous basis. I therefore summarize by offering as diagnoses, with a certain amount of trepidation: tabes, old and inactive; arsenical peripheral neuritis, with toe drop—I do not know if he still had it at the last entry because they did not mention a neurologic

examination; cor pulmonale, with congestive failure the cause of death; some form of pulmonary fibrosis, possibly, adrenocortical insufficiency, more likely due to tuberculosis than to syphilis. I do not believe that one need mention cancer, although the adrenal glands are sometimes involved by a malignant process. I cannot find any evidence of cancer, so I think that it can be ruled out.

DR. DONALD KING: I saw this man in consultation with Dr. Kite. On the basis of this first film, as Dr. Hampton said, I thought he probably had enlarged lymph nodes at the hilus. I sent him in with the idea that it might be lymphoma and that x-ray treatment might relieve the pressure.

I do not believe that the cyanosis of the upper part of the body, as distinguished from the rest of the body, was very marked.

DR. TRACY B. MALLORY: Sometimes, in simple cases of emphysema, it is more marked in the upper half of the body than in the lower half; I do not know why.

DR. KING: The roentgenologist who went over the films and did the fluoroscopy said that the shadows were pulmonary arteries and not lymph nodes, and that settled that. Then the question came up concerning the condition in the vascular bed in the lungs. Experience has shown that it is difficult to distinguish between plain pulmonary arteriosclerosis without narrowing of the lumen, obliterating endarteritis and thrombi. Dr. Bland saw this man in consultation. I forget which of these diagnoses he chose, but I think that it was obliterative endarteritis.

DR. EDWARD F. BLAND: I chose that, but I think we overlooked the leukocytosis and the paroxysms that Dr. Means has brought out. I might say that we saw him just before he died, and we did not have quite the problem that Dr. Means had in dealing with the past history. He was a very ill man, with obviously extreme cor pulmonale, distended neck veins, congested liver and the x-ray findings described; when it was all added up, we chose between two possibilities—obliterative endarteritis and thrombi.

DR. KING: The patient probably did not have pulmonary fibrosis from the x-ray standpoint.

DR. HAMPTON: I do not believe he had enough to produce cor pulmonale. It is chiefly confined to the upper lobes. The lower lobes are very good. The change in the bases of the lungs over a period of a month are further evidence that the process was more acute.

DR. PAUL D. WHITE: What was your second choice, Dr. Bland,—thrombosis of the pulmonary vessels based on emphysema?

\*White, P. D. *Heart Disease*. 931 pp. New York: Macmillan Company, 1931. Pp. 404-409.

DR. BLAND: We could not find any source for emboli.

DR. HAMPTON: These shadows are quite like those of pulmonary infarcts.

DR. WALTER C. KITE: I think it has not been emphasized that all the neurologic symptoms were unilateral, all on the right side. The cyanosis and the dilatation in the neck did not develop until five days before death. This man was in the office at work one week before Dr. King first saw him.

DR. KUBIK: When this patient was studied here, about three and a half years before he died, a presumptive diagnosis of *tabes dorsalis* was made. At that time, there was not much weakness. The patient had been complaining of numbness or paresthesia, and there was some analgesia, as well as impairment of vibratory and position sense. The Argyll-Robertson pupils influenced us a great deal, as they did Dr. Means. The later course, marked by the development of foot drop, and the marked weakness, with some atrophy, did not fit in with *tabes*. I believe that the patient was seen later at the Boston City Hospital, where a diagnosis of peroneal muscular atrophy was made. When he was here, we did think of the possibility of hypertrophic interstitial neuritis, but could not find any hypertrophy of the peripheral nerves and concluded it probably was not that.

#### CLINICAL DIAGNOSES

Pulmonary endarteritis.  
Cor pulmonale.  
Heart failure, right-sided.  
*Tabes dorsalis*?

#### DR. MEANS'S DIAGNOSES

Chronic cor pulmonale.  
Congestive failure, right-sided.  
Pulmonary fibrosis (<sup>2</sup> type).  
*Tabes dorsalis*, old.  
Arsenical neuritis, old?

#### ANATOMICAL DIAGNOSES

Degeneration of spinal-nerve roots.  
Secondary degeneration of posterior columns.  
Thrombosis, left popliteal vein, old.  
Embolism and thrombosis of pulmonary arteries, old and recent  
Cor pulmonale.  
Infarcts of lungs, healed.  
Chronic passive congestion  
Ascites.  
Pulmonary tuberculosis, inactive.

#### PATHOLOGICAL DISCUSSION

DR. MALLORY: The post-mortem examination showed a considerably enlarged heart; nearly all the enlargement was on the right side, the right ventricle was nearly twice as capacious as the left, and in spite of the dilatation, it measured 7 mm. in thickness. The pulmonary arteries showed clots of all ages, some quite fresh and some evidently very old, completely organized and extensively recanalized. These were present in the major and intermediate-sized arteries, and the small arterioles throughout the lung were entirely normal. The picture suggested to us multiple embolism, with perhaps secondary retrograde thrombosis and primary pulmonary endarteritis. As a possible source for this, there was an extensive old thrombophlebitis of the left iliac vein. Will you continue with the neurologic findings, Dr. Kubik?

DR. KUBIK: There was marked degeneration of the calf muscles, presumably secondary to disease of the anterior spinal roots or of the spinal roots and anterior horn cells. Both anterior and posterior spinal roots of the cauda equina were enlarged. Many of them were two or three times the normal size. Microscopic sections showed that the enlargement was due to interstitial tissue; the fibers were actually diminished in number. The remaining ones were in process of degeneration. There was degeneration in the posterior column, which, I should say, was secondary to degeneration of the posterior roots. I am not altogether sure about the findings in the anterior-horn cells. Many of them exhibited changes that were unquestionably secondary to the degeneration of the anterior roots (axonal reaction), but I could not be sure that there was not also some primary degeneration. It will require further study to establish a diagnosis. Peroneal muscular atrophy (Charcot-Marie-Tooth disease) is a possibility, and perhaps hypertrophic interstitial neuritis also has to be considered, even though there was no hereditary or familial history.

DR. MEANS: What were the Argyll-Robertson pupils due to?

DR. KUBIK: I cannot answer that. The mid-brain has not yet been examined.

DR. MEANS: Did your neurologic examination exclude ordinary *tabes*? You told us that you did not know what to call it, but can you say it is not *tabes*?

DR. KUBIK: Almost certainly not. In *tabes*, the anterior roots are of normal size, and the posterior roots are very small.

DR. MEANS: Was there any evidence of tuberculosis?

DR. MALLORY: There was inactive apical tuberculosis, not progressive.

DR. MEANS: Were the adrenal glands normal?

DR. MALLORY: Yes.

### CASE 28092

#### PRESENTATION OF CASE

*First admission.* A sixty-three-year-old housewife was admitted to the hospital because of a fainting spell.

She had suffered recurrent episodes of abdominal pain for many years. These attacks, which were described as crampy, colicky and associated with "gas," started in the left upper quadrant, and occasionally radiated over the lower ribs or down the left arm and to the left subscapular region. The pain was never substernal. There was no nausea or vomiting, and the bowels had always been regular. In the year before entry, the discomfort seemed to follow exertion, although this was not always so. The patient was able to relieve the pain by raising or swinging her arm, or by taking nitroglycerin. At times, she took bismuth and restricted her diet, and passed several weeks without pain. On the evening of admission, an attack came on while the patient was attending a concert. She took a tablet of nitroglycerin, and shortly afterward fainted.

The family history was irrelevant, and the past history complicated. The patient had had severe varicella when thirty-nine years old. At forty-one, she had had the uterus removed for prolapse. Two years later, the gall bladder had been removed for "pain"; gallstones were found at the operation. Hemorrhoids were removed at the age of fifty-one, yet the patient noted occasional bright-red blood in the stools in the year preceding entry. Eight months before admission, roentgenographic examination, including a barium enema and a gastrointestinal series, showed "diverticulosis of the large bowel."

Physical examination showed an obese woman in no distress. The chest showed evidence of old rickets. The heart was of normal size, with a very soft systolic murmur of the apex, and a loud, ringing aortic second sound. The lungs were clear. There was slight, diffuse tenderness in the abdomen, most evident in the left upper quadrant. The liver edge was palpable one or two fingerbreadths below the costal margin.

The temperature was 97°F., the pulse 75, and the respirations 24. The blood pressure was 160 systolic, 90 diastolic.

Examination of the blood showed a white-cell count of 5900. The urine showed a + test for

albumin, with 50 white cells per high-power in the sediment.

An electrocardiogram showed sinoauri bradycardia, with a rate of 50. The P waves PR intervals were normal. There was slight ring of the QRS complexes, and marked left deviation, with inversion of all complexes Lead 3.

The patient was discharged on the second

*Second admission* (nine months later). Six months after discharge, the patient fell down and fractured her left shoulder. Because of injury, she lay on her right side frequently, a position that seemed to bring on the customary attack of abdominal pain. A month later, the left ankle was broken in another fall. A month after this, one of the episodes of abdominal discomfort was followed abruptly by radiation of tearing "tearing" pain downward over the whole left into the pelvis. The patient felt nauseated, dizzy, and vomited. There were no chill or fever. Nitroglycerin afforded no relief. After an hour and a half, a physician gave her a hypodermic injection. The severe pain went away gradually within half an hour, but an ache was then noted in the arms below the shoulders. There was gradual onset of numbness and weakness in both legs, progressing to anesthesia, paralysis within two hours. The patient was able to urinate or defecate. In retrospect, the patient stated that her left leg had seemed colder than the right for several months before this attack.

On re-examination, the patient again appeared in no acute distress. The heart and lungs were essentially as before. The abdomen was distended. The liver edge lay two to three fingerbreadths below the costal margin. There was total loss of sensation in the lower extremities and abdomen below a level corresponding approximately to the level of the insertion of the diaphragm. The upper limit of this area of anesthesia shaded off gradually rather than sharply. The skin over the region involved was of normal color. Voluntary movements of the lower extremities were abolished. Deep tendon reflexes and abdominal reflexes were absent. Stimulation of the soles of the feet produced slow mass flexion and extension reflexes in the whole lower extremities.

The temperature was 100.5°F., the pulse 110, and the respirations 20. The blood pressure was 110 systolic, 60 diastolic, in each arm.

Examination of the blood showed a white-cell count of 9200 with 83 per cent polymorphonuclear cells, and a red-cell count of 4,000,000 with 15 gm. hemoglobin. The serum protein was 5.5

per 100 cc. The urine showed a + test for albumin, with occasional red cells in the sediment.

An electrocardiogram was quite similar to that obtained on the first admission, except for increase in amplitude of T<sub>2</sub> and T<sub>3</sub>, without, however, any characteristic shape.

A roentgenogram of the thoracic spine showed no evidence of vertebral disease. The entire thoracic aorta was tremendously enlarged. The aortic knob, 10 cm. in diameter, displaced the trachea toward the right. There was calcification in the inferior rim of this knob, and a line of calcification in the wall of the descending aorta, lying well out toward the axillary line. The heart shadow showed prominence in the region of the left ventricle. The lung fields were clear.

Lumbar puncture yielded clear colorless fluid under initial pressure of 145 mm. Microscopic examination showed 454 red cells and 1 white cell per cubic millimeter. The total protein was 52 mg per 100 cc. The gold sol curve was 1233411000. There was insufficient fluid for a test of the Wassermann reaction.

On the second hospital day, the temperature fell to 98°F, and the pulse and respirations continued as before. The patient felt prickling in the legs and feet, especially on the right, but there was a slow further return of protopathic sensation. Bilateral Babinski plantar responses gradually appeared. Subsequent roentgenograms of the chest showed essentially no change. From time to time, there were transient elevations of temperature to 100°F. Tidal drainage of urine by catheter was maintained. There was intermittent bacilluria, which responded fairly well to sulfadiazine therapy. The patient was discharged after ten weeks, unimproved.

At home, the slow return of sensation continued, but there was no return whatever of motor control. The patient continued to have frequent bouts of pain, which appeared to originate in the left upper quadrant but radiated to the region of the left scapula and, on one occasion, to the right shoulder. The pain was often severe enough to make her break out in a perspiration. It could sometimes be relieved by lying on the left side. Relief from the pain was sometimes accompanied by an audible gurgling in the left flank. Two months after discharge, the patient awoke one morning with severe knifelike pain about her left shoulder and under her left scapula. She felt faint and vomited. The pain was gradually relieved after a hypodermic injection of morphine. In the late afternoon of the same day, the pain returned, and the patient rapidly went into severe shock and gradually became comatose. She died five hours after this second attack of pain.

## DIFFERENTIAL DIAGNOSIS

DR FRANCIS R. DIEUAIDE. We have an elderly woman who had two sets of attacks of pain. One of these comprised colicky pain, which radiated usually into the left upper arm and to the left shoulder and was said to have been present for many years. There were two major episodes of extreme pain, the first of which is described as "tearing," along the left side down to the pelvis. It grew out of one of the attacks of the previous series. It was associated with paraplegia. The second attack was knifelike pain about the left shoulder and under the scapula, followed by death in five hours. These two discrete attacks strongly suggest pain of vascular origin. We also know that there were marked changes in the vessels in the x-ray picture. As to the paraplegia, we are given no sign of interference with circulation in the legs. On the whole there is little doubt that the difficulty was of cordal origin. There were two recent fractures. The question might be raised whether they were pathologic fractures and whether the patient had a neoplasm somewhere, but there is no evidence of that and we are directly told that there was no sign of fracture in the vertebral column. I suppose one should also raise the question whether the difficulty might have been due to metastases in the cord itself, but there is no reason to think of that in the face of the other information; furthermore, we must note the improvement in sensory function, which apparently was quite good, although there was no return of motor function. Everything considered, I think one might easily come to the conclusion that these cord changes were probably due to a vascular disturbance. The two major attacks of pain might possibly suggest coronary pain—associated with myocardial infarction, perhaps; but the description is somewhat peculiar, especially the radiation in the first attack to the pelvis. Such radiation happens occasionally, although rarely. Coronary difficulty offers no explanation for the cord changes. The blood pressure was well sustained, although it did fall somewhat. The electrocardiogram was normal, except for sinoauricular bradycardia. This is very much against a diagnosis of coronary occlusion with myocardial infarction.

An aneurysm of the ordinary vascular sort might possibly account for the recurrent pain, but I do not believe that such an aneurysm could account for the two discrete attacks described. We have no evidence for syphilitic aneurysm, no positive blood or cerebrospinal fluid Wassermann reaction. The spinal fluid was essentially normal. It was contaminated with a little blood, but that is enough

to produce the gold-sol changes, even though the fluid was colorless.

Of course, this might have been an arteriosclerotic aneurysm; the patient was an elderly woman, and that is a possibility. Furthermore, the calcification in the x-ray pictures speaks directly for that because calcification of that sort is not likely to be present in syphilitic aortitis. The blood pressure speaks somewhat for an arteriosclerotic process. Then we have dissecting aneurysm. The description of the first attack fits very well, I think, into the usual description of dissection, although arm radiation is not nearly so common as it is in myocardial infarction. It is, however, described in some cases; I do not believe that it is against the diagnosis. The maintenance of blood pressure is in favor of it, and the cord changes are particularly in favor of it.

May we see the x-ray films?

DR. TRACY B. MALLORY: There is no radiologist present.

DR. DIEUAIDE: I hesitate to say just what this shadow is, but it is evidently the outline of a vascular swelling of some sort, derived from the aorta and extending far to the left. I doubt if, at a distance, one can see the calcification, but there is a good deal of it spread out in a large semi-circular arc well to the left of and below the usual site of the aortic knob. With these x-ray films, in addition to the story, one would, I think, be going out of the way not to concentrate on dissecting aneurysm.

In recent years, we have heard a great deal about dissecting aneurysms in aged people, more commonly perhaps in men, but still not rarely in women. The dissection frequently occurs after exertion, but not necessarily. It is sometimes symptomless, a double aorta being found only by post-mortem examination. The blood pressure is usually relatively maintained in patients who do not succumb. I am inclined to think that this patient had dissection of the ordinary type, based on media necrosis cystica.

The cord changes are of special interest in connection with dissecting aneurysm, if we are right about the diagnosis. They have been recently emphasized by Tuohy et al.,\* who stressed the patchy, transient character of the symptoms, and the frequent occurrence of coldness and numbness. The changes described here are severer. We are interested especially in the persistent, complete loss of motor function. I have no explanation for that. I am sure that someone else will be able to tell us about the circulation of the lower cord. As I understand it, it is a little more vulnerable

than circulation of the upper cord, because blood is supplied to the upper part by the vertebral arteries, whereas the lower cord has only the branches of the aorta, the intercostal and sacral arteries. If this diagnosis is correct, the lesion should have extended down into the abdomen so that it cut off the blood supply of the lower part of the cord. At the same time, other vessels might have been affected, such as the renal artery. We have no particular evidence of that in this case.

The second attack of pain on the last day speaks for rupture of the dissection. Dissection usually begins in the upper mediastinum. If the patient had a dissection, since there was pain about the left scapula, I should first think of the mediastinum as the site of the rupture.

The preceding series of attacks offer me some difficulty. The attacks for many years were centered in the left upper abdomen, a somewhat unusual site. Did the patient have diverticulosis? In any event, I do not think chronic diverticulitis is a likely explanation. The gurgling that occurred when the patient had relief of pain does not mean much to me. The pain might suggest a second serious lesion, such as carcinoma of the colon but this is unlikely. I suppose one should mention diaphragmatic hernia. The pain is quite permanent for that, and we ought to be able to see a hernia in the x-ray film. The patient apparently acquired a urinary-tract infection, but these attacks do not sound much like renal pain. The radiation was upward instead of downward, as it usually is in renal pain. Were they attacks of anginal pain? The reasons mentioned before are still against that. Relief by nitroglycerin does not prove anything. Relief by swinging the arm is also rather against angina. I think that the patient must, of course, have had an antecedent aneurysm before the dissection, an unusually large one to be caused by atheroma. Somehow, these attacks of pain were produced by this aneurysm which I should guess to have been in the first portion of the descending thoracic aorta. So that I think the patient had the following conditions: an old arteriosclerotic process with hypertension although there is not much evidence of that, and an unusually large arteriosclerotic sac—perhaps. I am passing up a chance to make a diagnosis of syphilitic aneurysm, but I do not believe so; a dissecting aneurysm, which went all the way to the neighborhood of the bifurcation of the aorta but not through it; and something like myelomalacia of at least the lower spinal cord, which seems to have affected the pyramidal tract particularly. I suppose there was also cystitis and perhaps pyelitis.

DR. WILLIAM B. BREED: It is strange that no

\*Tuohy, E. L., Boman, P. G., and Berdez, G. L. Spinal cord ischemia in dissecting aortic aneurysm. *Am. Heart J.* 22:305-313, 1941.

serologic findings are recorded. I should be interested in knowing what they were.

DR. MALLORY: There was no record of them. The patient's physician checked over his records and also corresponded with other doctors who had seen her. I think it was one of those cases in which each one assumed that the other had done it.

DR. EDWARD F. BLAND: This patient's history and x-ray films were presented at Grand Rounds in the Ether Dome. Some of you may recall it. Dr. Michelsen discussed the cord difficulty. At the time, all were quite convinced that this must be a dissecting aneurysm or some modification of it. I think there was only one dissenting voice, and that was from the pathologist who was present — Dr. Castleman. He wondered if the size of the aorta by x-ray study did not suggest the likelihood of something else than a simple dissection. There were one or two other interesting points that Dr. Castleman raised about the presence of calcification of the aorta. Perhaps he would comment on that now.

DR. BENJAMIN CASTLEMAN: We had never seen a dissecting aneurysm in the presence of marked arteriosclerosis and calcification. Also, the patient did not have hypertension. Although dissecting aneurysms have been recognized on x-ray examination, they do not produce such marked dilatation of the aorta as was seen in this patient.

A PHYSICIAN: I had seen her for three years, and she never had a systolic blood pressure over 160 during that time.

DR. MALLORY: The great majority of the cases that we have seen have had a definite hypertension. One case of Dr. Fremont-Smith's that we presented recently had very little, however.

DR. JOST MICHELSEN: There was little doubt from the onset that the cord lesion was a vascular affair, and the dynamics during lumbar puncture were quite normal. The return of sensation was really very slight — practically none at all. I wonder why Dr. Dieuaide used the term "contamination" of the cerebrospinal fluid. Four or five hundred red cells may be found in cases of vascular obliteration, and are consistent in this case with arterial occlusion, which caused the softening of the cord.

#### CLINICAL DIAGNOSES

Dissecting aneurysm, with apoplexy of cord at the fifth dorsal segment.

Obesity.

Diverticulosis.

#### DR. DIEUAIDE'S DIAGNOSES

Extensive atheroma of aorta, with aneurysm.

Dissecting aneurysm.

Myelomalacia of lower spinal cord.

Cystitis or pyelitis?

#### ANATOMICAL DIAGNOSES

Aneurysm of descending aorta, probably syphilitic, with rupture.

Hemothorax, left

Arteriosclerosis, severe, aortic and coronary.

Infarction of spinal cord.

Operative scars: cholecystectomy and hysterectomy.

#### PATHOLOGICAL DISCUSSION

DR. MALLORY: At post mortem examination, a very large fusiform aneurysm of the descending aorta was found. It began just beyond the arch and extended nearly down to the diaphragm. It was filled with a laminated thrombus, which appeared to cover the mouths of the intercostal arteries; it seemed rather surprising that more of them were not obstructed. The aneurysm had ruptured into the left pleural cavity, which contained about 1500 cc. of blood, and the lung on that side was totally atelectatic. There was no dissection. The question then arose whether this was an arteriosclerotic, senile aneurysm or a syphilitic aneurysm. We have no serologic findings to bear on the point, so that we have nothing to go on but the microscopic appearance of the aorta itself. I do not believe that all members of the department are entirely unanimous as yet, but as I studied it I should have to call it syphilitic. There were marked focal destruction of the elastica in the media, collars of lymphocytes around the vessels in the adventitia, and sizable collections of plasma cells in the adventitia, which I should take more seriously. The ascending aorta was absolutely smooth and normal, and that is unusual in cases of syphilis. Sections of the ascending aorta were entirely normal. If I had to make a decision on the case, I should vote for syphilitic aneurysm. Dr. Kubik will tell us about the cord.

DR. CHARLES S. KUBIK: There was a softening of the cord, beginning at about the fifth thoracic segment and extending down into the midthoracic region. The lower part of the cord was normal.

The cord receives its blood supply from two sources: from the anterior spinal artery, which branches from the vertebral arteries, and from branches of the intercostal arteries. The anterior spinal artery did not provide an adequate blood supply in this case when the intercostals were blocked off by the lesion of the aorta. I do not recall another case like this.

DR. MALLORY: There was enough sclerosis in the coronary arteries for the patient to have had angina. The other possibility is that the attacks of colic were tabetic crises.

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established in 1828

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND  
PUBLISHED UNDER THE JURISDICTION OF THE  
COMMITTEE ON PUBLICATIONS

Official Organ of  
THE MASSACHUSETTS MEDICAL SOCIETY  
and  
THE NEW HAMPSHIRE MEDICAL SOCIETY

## EDITORIAL BOARD

Joseph Garland, M.D.	Stephen Rushmore, M.D.
William B. Breed, M.D.	Henry R. Viets, M.D.
George R. Minot, M.D.	Robert M. Green, M.D.
Frank H. Lahey, M.D.	Charles C. Lund, M.D.
Shields Warren, M.D.	John F. Fulton, M.D.
George L. Tobey, Jr., M.D.	A. Warren Stearns, M.D.
C. Guy Lane, M.D.	Dwight O'Hara, M.D.
William A. Rogers, M.D.	Chester S. Keefer, M.D.

## ASSOCIATE EDITORS

Thomas H. Lanman, M.D.	Donald Munro, M.D.
Henry Jackson, Jr., M.D.	

Walter P. Bowers, M.D., EDITOR EMERITUS  
Robert N. Nye, M.D., MANAGING EDITOR  
Clara D. Davies, ASSISTANT EDITOR

SUBSCRIPTION TERMS: \$6.00 per year in advance, postage paid, for the United States (medical students, \$3.50 per year); Canada, \$7.04 per year, Boston funds, \$8.52 per year for all foreign countries belonging to the Postal Union.

MATERIAL for early publication should be received not later than noon on Friday.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston, Massachusetts.

## PROCUREMENT AND ASSIGNMENT SERVICE

In these times of stress, physicians, as well as everyone else, are considering how they can best serve the Nation, and from the point of view of medical service, many factors must be taken into account. There seems little doubt that eventually nearly all male physicians under forty-five years of age who are physically and educationally qualified to enter military service will be inducted, but due regard must also be paid to the medical needs of other governmental agencies, state, county and municipal institutions, nongovernmental hospitals, medical schools, industry and, last but not least, civilian communities.

With all this in mind, the House of Delegates of the American Medical Association, at its meet-

ing in Cleveland last June, recommended to the Government that a procurement and assignment agency for physicians be formed, and on October 31, 1941, the creation of the Procurement and Assignment Service for Physicians, Dentists and Veterinarians, a subdivision of the Office of Defense Health and Welfare Services of the Office for Emergency Management, was authorized by the President. This agency is specifically instructed "to receive from various governmental and other agencies requests for medical, dental and veterinary personnel, to secure and maintain lists of professional personnel available, showing detailed qualifications of such personnel, and to utilize all suitable means to stimulate voluntary enrollment, having due regard for the overall public health needs of the Nation, including those of governmental agencies and civilian institutions." In accordance with the suggestion of the House of Delegates, the Directing Board is composed of five civilian practitioners,—four physicians and one dentist,—the chairman being Dr. Frank H. Lahey, of Boston, president of the American Medical Association.

Owing to the proximity of the creation of the Procurement and Assignment Service and the declaration of war on December 8, the bare skeleton of the necessary working force of the central office in Washington had only been established when it was flooded with requests for personnel from the military services and governmental agencies and for information from physicians, dentists and veterinarians. The demand for personnel resulted in an appeal for physicians who were immediately available for military service, and the response was so satisfactory that these needs have been met. It has been impossible, however, to answer the letters requesting information, and the Directing Board of the Procurement and Assignment Service decided that all existing pertinent facts should be made available to physicians, dentists and veterinarians. Much of this material has appeared from time to time in the *Journal of the American Medical Association* and the state medical journals; but there has been little continuity, and many of the basic regulations have subsequently been changed. Hence, the article in the February 21

issue of the *Journal of the American Medical Association* that describes the functions and activities of the Procurement and Assignment Service, gives recommendations based on current regulations and furnishes additional miscellaneous information should be carefully read by all members of the medical profession

Subsequent planning for the provision of military personnel and for the protection of nonmilitary medical services demands more facts than are now in the hands of the Procurement and Assignment Service, which consist chiefly of data taken from the questionnaires sent out by the American Medical Association over a year ago. State, district or county and local committees must prepare lists of essential personnel, which are based on the needs of industry, medical schools, hospitals and communities. But what is even more important, exact up to date information concerning the status of all physicians must be obtained. Within a few weeks, the Procurement and Assignment Service will forward a questionnaire to every physician, dentist and veterinarian within the United States. Furthermore, this will be accompanied by an enrollment form, whereby the physician, dentist or veterinarian, by signing up with the Procurement and Assignment Service, can express his willingness to help in the present emergency and can indicate his preference for service.

When the questionnaire is received, *all registered physicians, regardless of age, sex, physical condition, educational qualifications and citizenship, should immediately fill it out and return it*. Enrollment is purely voluntary, but in view of the criticalness of the war situation, it is difficult to comprehend how any physician can fail to offer his services to his country—ENROLLMENT SHOULD BE ONE HUNDRED PER CENT!

## EXAMINATION OF SELECTEES

UNTIL very recently, selectees have been examined by physicians of the Selective Service boards and, if

classified by them as fit for general military service, have been sent within a few weeks to an induction center, whose physicians work directly under the supervision of the Army of the United States. Selectees were sent to the induction centers on the assumption that they were physically and mentally fit and that they would be immediately sworn into the Army and sent to camp. Unfortunately, this was not the case. Approximately 18 per cent of the men were rejected because of the findings of the examiners at the induction centers, yet these men had had, perforce, to give up the positions in which they were employed and returned to their homes without a job and marked, in a way, as unfit. Furthermore, employers did not always distinguish between ability to hold down a civilian job and that to stand the rigors of combat service.

This has all been changed—and for the better. Selectees are examined by their local examining boards only for "gross disqualifying defects." If none are found, the men are, at some later date, sent to an Army examining or induction center. If they are then found to qualify fully for "general military service," they are returned to their homes with such knowledge and with the opportunity of rearranging their affairs before being called to camp some weeks later. If rejected, the causes of their defects are explained in simple language, and they are admonished to consult their personal physicians, if there is such a need. The burden on the Army physicians is, of course, greater, and their task more difficult, but the local board physicians—who generously donate their services—are relieved of much responsibility, and the selectee is in a far better position to arrange his own private affairs, come what may.

It is further hoped that some form of rehabilitation may find its way, officially, into this program. There are thousands of men with remediable defects who could, with appropriate aid, become fit for general military service and, by the same token, even better qualified to carry on in civilian life. Such rehabilitation is at present voluntary. It may and should become compulsory.



## OBITUARY

## KENNETH DANIEL BLACKFAN

1883-1941

Kenneth Blackfan began his career in medicine in the year 1905 as a country doctor. Eighteen years later he became Thomas Morgan Rotch Professor of Pediatrics, and for another eighteen years he carried his department forward with consummate skill and success. There is no need to recount to this faculty his large services to the Harvard Medical School. But, in order that our admiration of him may be complete, the record of a continuous and hard-won education which brought the country practitioner to a position of high effectiveness in university medicine should be before us.

He was born and spent his boyhood in Cambridge, New York, a pleasantly situated hamlet about forty miles north of Albany. On graduating from the local high school, he entered the Albany Medical School of Union University. During his third year, Richard Pearce came to the school as professor of pathology and bacteriology. Kenneth Blackfan responded to the enthusiasm of this fine student of disease. He begged, and won, permission to work in his laboratory through the following summer. A warm student-master friendship sprang up. This friendship determined his future course in medicine. But not immediately. On receiving his medical degree at the age of twenty-two, he returned to his home town and for the next four years drove about the countryside on the varied errands of a general practitioner. He always recalled those horse-and-buggy years with pleasure, and there are older citizens of that region who still delight in relating therapeutic triumphs of "young Doctor Ken." But there were disturbing visits to nearby Dorset, just over the line in Vermont, where Richard Pearce spent his summers. There he found friendly interest and encouragement, which gradually produced the determination to find out what might lie over the horizon in medicine.

So, in the year 1909, the young country doctor set out for Philadelphia with letters from Richard Pearce. There he was kindly received by Samuel Hamill and David Edsall, and a place was soon found for him as resident-in-charge of a foundling hospital. Kenneth Blackfan thereupon became a pediatrician. Two years later, John Howland, who had accepted the professorship of pediatrics in the newly reconstructed medical school of Washington University, offered him a residency. This was a very large stroke of fortune. It removed the adventurer from his lonely post in the foundling

hospital and, after two years in St. Louis, placed him in the group of young pediatricians who assembled around Howland in Baltimore when he succeeded Von Pirquet at Johns Hopkins in the year 1912. Here there was a newly built hospital for infants and children, and laboratory equipment far beyond anything which had yet been given a clinical department in this country. Howland's group used their large opportunity with enthusiasm, and under his wise guidance, the laboratories were from the outset importantly productive. It was the place to be in pediatrics at that time. The most beloved member of this group was the resident physician. No one watched work under way in the laboratories with a more eager interest. And he found time to participate. By way of instance, his work with Dandy on internal hydrocephalus has come to deserve that lofty adjective, classic. His demonstration that dehydration is a much more dangerous feature of diarrheal disease than is the state of acidosis, which Howland and Marriott had just discovered, shifted emphasis from alkali therapy to fluid replacement and produced the basis of our present effective treatment of this chief scourge of infants.

When Kenneth Blackfan reached the age of thirty-seven, he was still a resident. He had held this modest post for eleven years. But he had reached his goal. He knew the existing body of knowledge in his chosen field, he knew its frontiers, and he knew where the paths of progress lay. He was a superb diagnostician and a master of detail of hospital care of patients. Behind all this, four years of countryside practice had given him resourcefulness in use of means at hand and an understanding of the social realities of the physician's task. He was in all respects qualified for the diverse duties of departmental headship. His first commission came in the year 1920, when he was appointed professor of pediatrics at the University of Cincinnati. There he built up his department and guided a large development of hospital equipment with outstanding success. Then in 1923 the fruits of eighteen years of education toward leadership fell to Harvard.

Why did he follow this long and economically narrow path with such serene contentment? This question would have annoyed Kenneth Blackfan. His philosophy was remarkably uncomplicated. There was nothing which could be called ambition, and there was nothing of the *ich dien* complex about him. He had simply discovered a durable delight in his work. The anatomy of this delight did not interest him. He knew an inscrutable phenomenon when he saw one. His modest and conservative use of a fine mind gave

his judgments a great validity and brought him into a high position in the councils of this school. Knowing little of the art of verbrige, he was not a skillful lecturer, but in the wards his teaching of students and of interns was close to perfection. He used the treasures of his experience, not to dazzle by making the diagnosis at a glance, but to point out sound appraisement of obtainable evidence.

A large cause of Kenneth Blackfan's success in leadership was his gentle friendliness. He always made his associates feel that they were his comrades in the enjoyable adventure against disease. Also, he was very brave. Beginning in his later Baltimore years, he suffered a series of physical afflictions which he bore with an unbelievable fortitude. He was friendly and gentle and brave. The simplicity and the sincerity of these traits gave him his great beauty of personality.

J L G  
J H M  
R M S

A resolution adopted by the Faculty of the Harvard Medical School, January 7, 1942

\* \* \*

Kenneth Daniel Blackfan, Thomas Morgan Rotch Professor of Pediatrics at the Harvard Medical School, chief of the Medical Service of the Boston Children's Hospital, medical director of the Infants' Hospital, wise counsellor to many, was born in Cambridge, New York, in 1883, the son of a country doctor. He was graduated from the Cambridge High School in 1901 and from the Albany Medical School of Union University in 1905, and after this minimal amount of formal education, became himself a country practitioner. From this realistic postgraduate course in the art of medicine, he emerged four years later, *summa cum laude*.

Turning his back at this point on general practice, he became resident in-charge at the St Vincent de Paul Foundling Hospital in Philadelphia, then resident pediatrician at the St Louis Children's Hospital, then, in 1912, resident pediatrician at the Harriet Lane Home and instructor in pediatrics at Johns Hopkins University School of Medicine. He was still at this post, in 1917, when the first world war stripped the country of its physicians. His associates left him, even to his chief John Howland, he himself was an officer in the Medical Reserve Corps but, afflicted with corneal ulcers following a Gasserian ganglion operation, was, of necessity, released from military service.

'They also serve who only stand and wait'  
Kenneth Blackfan remained in Baltimore and,

almost single handed, with the help of his students, carried the department and the Harriet Lane Home through the war years.

In 1917, he was made an associate and, in 1919, associate professor of pediatrics. The following year he became professor of pediatrics at the University of Cincinnati, where he remained until the call to his last post, with us, in 1923.

Labors fall in good measure upon willing shoulders, and Kenneth Blackfan bore his share of them uncomplainingly, and the honors that sometimes accompany them, unassumingly. Among other obligations that he accepted after coming to Boston were, in 1925, the presidency of this society and, for the three succeeding years, membership on its council.

After he had spent those years in the wilderness of private practice, with the intellectual diet of locusts and wild honey that accompanied them, his activities became more diversified, being divided among clinical, investigative and administrative medicine, always with teaching. It is with these four major activities in mind, but with his personality in the foreground, that we do honor to him now and record these simple facts.

A good tree cannot bring forth evil fruit, neither can a corrupt tree bring forth good fruit.

Wherefore by their fruits ye shall know them

Matthew VII 18-20

J G

A resolution adopted at a meeting of the New England Pediatric Society on January 14, 1942

## MEDICAL EPONYM

MURPHY BUTTON

On October 15, 1892, Professor John Benjamin Murphy (1857-1916) read his first description of this article before the Mississippi Valley Medical Association, and the paper appeared under the title Cholecysto-intestinal, Gastro-intestinal, Enterointestinal Anastomosis and Approximation without Sutures (Original Research) in the *Medical Record* (42: 665-676, 1892).

To overcome these obstacles and thus lessen the risk to the life of the patient, I have devised a mechanical means to dispense with the need of sutures the necessity of invagination the possibility of non apposition the sloughing through of disks the digestion of the catgut, the almost unsurmountable difficulties of technique of operation, the prolonged and fatal exposure of the abdominal contents and the protracted anastomosis. How much I have accomplished by my labor I desire you to be the judges after I have demonstrated to you the results of my experiments and performed for you a gastroenterostomy and an end-to-end approximation of intestine by means of the device I here present to you to be known as the Anastomosis Button.

R W B

## MASSACHUSETTS MEDICAL SOCIETY

## COMMITTEE ON MATERNAL WELFARE

## OBSTETRIC ROUTINES

No one can tell how seriously the national emergency will influence hospital nursing, but much of the refinement that has come to be regarded as necessary will have to be eliminated. It is not at all unlikely that many obstetric services will very seriously feel the shortage of nurses; however, if well-trained and efficient head nurses can be retained, such services can be staffed by younger and less experienced nurses. If this situation eventuates, and something of the sort undoubtedly will, the fewer drugs there are in the medicine cabinets the simpler their administration will be, and the fewer the mistakes made. Furthermore, such a policy will cut down on expense.

Laboratory investigation has proved that skin disinfection at the time of labor can no more adequately, or perfectly, be accomplished than by the use of ether and a 1 per cent iodine solution. The same combination has also been used for a long time, with perfect success, for preparation of the abdomen for laparotomy. The cost of this solution, depending on the market value of alcohol, is about 13 cents a pint. The formula of the solution is as follows: potassium iodide, 1 gm.; iodine, 1 gm.; and alcohol (95 per cent) up to 100 cc. The most economical way of applying the solution is to use a spray. A No. 15 DeVilbiss atomizer, with a nasal applicator, has proved to be satisfactory. For the preparation of the skin, when it is desirable to cause no discomfort, a watery solution of Zephiran is suggested. It is advised that no other solutions for skin disinfection be used in the delivery rooms.

The objection that iodine causes burns and so should not be used has been proved false, over a long experience, especially when such a weak solution is employed. Iodine may cause an occasional burn, but so may other skin disinfectants. Diabetic patients are said to have very sensitive skins; however, in a long experience with diabetic patients, no skin burn of any particular degree has occurred.

Because of the sensitiveness of the skins of some diabetic patients, the use of zinc oxide adhesive tape has been discontinued. Since in a large general hospital the use of zinc oxide tape, for the purpose of holding dressings on surgical wounds, must be a great expense in the course of a year, and since it is imperative that all savings be considered, it is suggested that this practice be discontinued. A gauze roll held in the stay sutures makes a satisfactory dressing.

Many preparations of ergot are on the market. If one standard preparation can be decided on for general use, it will make for a simpler, easier-running service. It is suggested that 1/320-gr. ampules of Ergotrate or Hypoloid Ergometrine be used intravenously and intramuscularly; these cost \$21.60 per hundred. Ergotrate or Ergometrine tablets, which cost about 4 cents apiece in thousand lots, are suggested as the sole ergot preparation to be used for oral administration. This routine has already been established in several hospitals in the Boston area.

It is also suggested that, because of the cost, thymol iodide *U.S.P.* be used solely in place of all other, and more expensive, dusting powders.

## RETIREMENT

Frank L. Morse, M.D., of Somerville, has recently retired after forty years' service with the Somerville Board of Health. He graduated from Harvard Medical School in 1894, and after three years at the Boston City Hospital, including two years as assistant resident physician at the South Department, was medical and sanitary inspector of the Massachusetts Board of Health from 1898 to 1905 and a district health officer from 1909 to 1915. From 1901 until his retirement from the Somerville Board of Health, he had been in charge of the bacteriologic laboratory, the contagious-disease hospital, contagious-disease control and all other medical work of the Board. He was discharged from active service in the United States Army in 1919, with the rank of lieutenant colonel, and was retired from the Officers Reserve Corps in 1935, with the rank of colonel.

## "CHILDHOOD ABDOMINAL SURGERY"\*

Not infrequently, when an abdominal operation is recommended for an infant or for a child, surprise is expressed by such a remark as, "I didn't know babies and children ever had such things," or doubt about the ability of the young to stand a surgical operation is indicated. So commonly are these ideas held that it has seemed wise to include some discussion of those conditions of the abdomen for which surgical treatment is desirable in the young.

The young differ from their elders in the frequency with which they are affected rather than in the types of their diseases. Thus, it has been stated correctly that the infant or child may present any of the surgical conditions recognized later in life, but that certain of them are very rare in the young and others are relatively common. The young differ also in their response to disease and may be prostrated seriously by an injury or infection sooner than adults would be. However, with appropriate treatment and management, their recuperative powers are tremendous, and their ability to heal and to repair damaged tissues is very great.

The first and most cheering point that I should like to make is that young persons are excellent surgical subjects, provided that the treatment is conducted by qualified surgeons, the hospital environment is adapted to the needs of infant and child, the anesthesia is well chosen and

\*A "Green Lights to Health" broadcast given through Station WAAZ by Dr. Henry W. Hudson, Jr., on December 6, 1941, and sponsored by the Public Education Committee of the Massachusetts Medical Society and the Massachusetts Department of Public Health.

administered skillfully, and the special instruments and equipment that may be necessary are available. Even a newborn baby will tolerate an abdominal operation of considerable magnitude. Indeed, a group of conditions seen in the newborn must be treated immediately by successful operation if the infant is to survive. These include certain errors in development prior to birth which result in inability to take or to retain nourishment. 'Diaphragmatic hernia' or so-called 'upside down stomach' and the several forms of obstruction of the intestinal tract are examples.

Not immediately but a few weeks after birth a peculiar form of obstruction to the outlet of the stomach is seen fairly often. The fundamental cause is not known but the effect is that the infant nurses hungrily only to vomit all the feeding within a few minutes. Untreated, these patients lose or fail to gain weight and present a pitiful appearance of emaciation as they hungrily cry for the food they cannot retain. In hospitals interested in such patients where large numbers are treated surgically, ninety nine out of a hundred are permanently cured by operation on the stomach.

Somewhat later, at about the sixth or seventh month of life, the largest number of cases of intussusception or telescoping of the intestine into itself occurs. Although this serious surgical emergency may be seen at any age curiously enough, it is much commoner in infants. Usually, there is sudden onset, with evidence of severe colicky pain causing the baby to draw his legs up, cry out and often become very pale. The pain comes at intervals with intervening periods of apparent well being, and mucus and blood may later be passed with the stool. Promptly recognized and operated on within twenty four hours of onset, practically all these patients may be saved but when there is delay the loss of life mounts tragically with the duration of the attack.

At all ages, hernias or ruptures of several types are seen, and the young patient is no exception. Nonoperative treatment is not likely to result in cure, and the mere existence of a hernia constitutes a threat of serious complications to any nothing of the inconvenience and discomfort that may be present. Some are inclined to temporize and delay operation for these patients but there is no reason why a baby or child who is otherwise well cannot be cured surgically at almost any age. The end results of operation for hernia appear to be better when operation is performed in early rather than in adult life.

In general one may say that the need for surgery results from one of several causes: errors in development of which the digestive tract obstructions and hernias are examples; injuries requiring surgical treatment—the abdomen may be the site of such an injury; automobile accidents, falls and injuries in schoolboy athletics that require operation for the repair of an injured organ or for the control of bleeding; although the relatively sheltered life of the young makes such accidents uncommon and infections of the peritoneum or membrane lining the abdomen and covering the several organs. Thanks to the discovery of chemical methods of treatment within the last few years there has been great improvement in the results of treatment and many lives are saved that would otherwise have been lost.

Surgery may also afford the only chance of relief from tumors. Some of the tumors produce mechanical effects, which may be relieved dramatically by surgical removal. It will perhaps surprise my listeners to learn that young persons may be the victims of cancerous growths but some of the most malignant tumors recognized are seen in the young. Certain of these are re-

moved by abdominal operations, and the urgent need of early recognition and treatment cannot be overemphasized.

It sometimes happens that the most careful examination and x-ray and other studies do not suffice to determine a diagnosis of conditions affecting the abdomen and its contents. An exploratory operation to permit actual visualization and handling of the organs may be desirable. Such a procedure, if recommended, should not be a reason for dread or great concern. It is safe to say that a properly conducted exploration in itself is accompanied by very little risk to health, and much may be gained by the determination that conditions are normal or by finding and correcting an abnormality.

No discussion of the subject would be worth while unless emphasis was placed on a condition that is most commonly the reason for abdominal operation and unfortunately and unnecessarily occupies a very important place in the list of causes of death in the young. I say unfortunately and unnecessarily because, ideally, no child should suffer a long illness or have his life jeopardized by appendicitis. To reach the ideal, two things are necessary: prompt diagnosis and early operation. Study after study from surgical clinics throughout the country has demonstrated that with early diagnosis and operation there is almost no loss of life, but with delay and the development of complications the picture is very different. Studies from several large clinics interested in the surgical problems of early life have also demonstrated that, aside from the difficulties in diagnosis, there is nothing peculiar to the young that should result in a high death rate from appendicitis. The same excellent results can be obtained in the young that can be obtained in adults provided three conditions are fulfilled. These are as follows: no cathartics or laxatives for children with undiagnosed abdominal pain, prompt medical observation for any child who complains of abdominal pain for more than an hour or two and prompt acceptance of the operation recommended if a diagnosis of appendicitis is made.

In my opinion, there is little place for the use of laxatives and cathartics, and they should never be employed for a young person with abdominal pain unless it is definitely known that appendicitis is not the reason for the pain. Such medication for a patient with appendicitis may well lead to early rupture of the appendix, which carries with it a number of very serious complications.

Appendicitis is a treacherous disease particularly in the young. It may occur at any age, even in infancy, and, after the first few years of life, becomes increasingly frequent until the age of twenty to thirty. It is particularly treacherous in children for three reasons because it is not thought of as a possibility, because it may be difficult to diagnose early, and because it often develops more rapidly in the young than in those who are older. It may occur coincidentally with or perhaps be related to certain infections such as colds, sore throats, measles and chicken pox, and its early symptoms of abdominal pain and vomiting are the common symptoms of many acute infections in childhood. There is only one safe rule and that is to regard the symptoms of abdominal pain and vomiting as possibly indicating appendicitis until competent medical opinion rules out this diagnosis.

Although most cases follow a pretty definite series of symptoms, there is still a wide variation that calls for careful thought and interpretation if a diagnosis is to be made before there are serious complications. Unfortunately, it is not possible to set forth a series of iron-clad rules to protect from disaster but it is worth while to

point out the usual symptoms and to correct certain misconceptions that experience has shown to be prevalent.

There need not be previous attacks or premonitory symptoms. The best time for operation is early in the first attack. It is seldom, if ever, wise to wait and see if the attack will subside—occasionally it may, but the risk is too great to accept. Appendicitis cannot be "frozen out" by an ice bag; indeed, only surgical treatment need be considered. The existence of some other condition, such as a cold, measles or chicken pox, does not mean that the child does not also have appendicitis. The pain need not be severe,—frequently it is, and this is fortunate, since it usually results in attention to the abdomen,—but often the pain is annoying, grumbling and persistent rather than severe and excruciating, and occasionally there is no complaint of pain at all. There is usually very little fever, commonly between 99 and 101°F., but this is subject to variations from a normal level up to 103°F. Again, abdominal tenderness is usually but not always apparent on examination, generally in the right lower part of the abdomen; however, it may be elsewhere, and any tenderness anywhere in the abdomen is always very significant. Sometimes, the tenderness is evident only after the physician has made an examination of the rectum. Vomiting almost always occurs after the onset of pain, but may precede pain or may be totally absent. A count of the white blood corpuscles is usually desirable to establish the diagnosis, but may be unnecessary—this is a matter for the physician to decide.

Finally, if your physician recommends operation for your baby or child, accept his advice with the assurance that there are many good reasons for such operations, and that under proper conditions the risk is very slight, and negligible when compared with the risk of withholding operation.

## MISCELLANY

### CONSERVATION OF SCHOLARLY JOURNALS

In 1941, the American Library Association created the Committee on Aid to Libraries in War Areas, headed by John R. Russell, librarian of the University of Rochester. The committee is faced with numerous serious problems and hopes that American scholars and scientists will be of considerable aid in the solution of one of these problems.

One of the most difficult tasks in library reconstruction after World War I was that of completing foreign institutional sets of American scholarly, scientific and technical periodicals. The attempt to avoid a duplication of that situation is now the concern of the committee.

Many sets of journals will be broken by the financial inability of the institutions to renew subscriptions. So far as possible, they will be completed from a stock of periodicals being purchased by the committee. Many more will have been broken through mail difficulties and loss of shipment, while still other sets will have disappeared in the destruction of libraries. The size of the eventual demand is impossible to estimate, but requests received by the committee already give evidence that it will be enormous.

With an imminent paper shortage, attempts are being made to collect old periodicals for pulp. Fearing this possible reduction in the already limited supply of scholarly and scientific journals, the committee hopes to enlist the co-operation of subscribers to the *Journal* in preventing the sacrifice of this type of material to the pulp demand.

It is scarcely necessary to mention the appreciation of foreign institutions and scholars for this activity.

Questions concerning the project or concerning the value of particular periodicals to the project should be directed to Wayne M. Hartwell, Executive Assistant, Committee on Aid to Libraries in War Areas, Rush Rhees Library, University of Rochester, Rochester, New York.

### RÉSUMÉ OF COMMUNICABLE DISEASES IN MASSACHUSETTS FOR JANUARY, 1942

DISEASES	JANUARY 1942	JANUARY 1941	FIVE YEAR AVERAGE*
Anterior poliomyelitis	2	0	1
Chicken pox	2275	1574	1861
Diphtheria	14	9	20
Dog bite	591	511	551
Dysentery, bacillary	6	3	13
German measles	130	63	60
Gonorrhea	357	263	376
Measles	1018	1887	1885
Meningitis, meningococcal	11	3	6
Meningitis, other forms	9	6	—
Mumps	2231	836	701
Paratyphoid infections	7	5	2
Pneumonia, lobar	390	1052	733
Scarlet fever	1401	596	819
Syphilis	417	296	414
Tuberculosis, pulmonary	222	269	299
Tuberculosis, other forms	19	27	26
Typhoid fever	8	4	6
Undulant fever	1	5	4
Whooping cough	1111	1076	1041

\*Based on figures for preceding five years

### GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Anterior poliomyelitis was reported from: Pittsfield, 2, total, 2.

Diphtheria was reported from: Billerica, 1; Boston, 3; Chelsea, 1; Fall River, 4; Lowell, 2; Shrewsbury, 1; Somerville, 1; Springfield, 1; total, 14.

Dysentery, amebic, was reported from: Marblehead, 1, total, 1.

Dysentery, bacillary, was reported from: Camp Edwards, 1; Salem, 1; Tewksbury, 3; Waltham, 1; total, 6.

Encephalitis, infectious, was reported from: Fort Devens, 1; Wellesley, 1; total, 2.

Lymphocytic choriomeningitis was reported from: Winchester, 1; total, 1.

Malaria was reported from: Cambridge, 1; total, 1.

Meningitis, meningococcal, was reported from: Amesbury, 1; Beverly, 1; Boston, 1; Cambridge, 1; Danvers, 1; New Bedford, 2; Norwood, 1; Springfield, 2; Winchendon, 1; total, 11.

Meningitis, other forms, was reported from: Boston, 5; Cambridge, 1; Greenfield, 1; New Bedford, 1; Reading, 1; total, 9.

Paratyphoid infections were reported from: Boston, 1; Gardner, 2; Malden, 1; Quincy, 2; Reading, 1; total, 7.

Septic sore throat was reported from: Barnstable, 1; Boston, 4; Burlington, 1; Cambridge, 3; Fall River, 1; Falmouth, 1; Gloucester, 1; Hanover, 1; Medford, 1; Newburyport, 1; Westford, 1; total, 16.

Tetanus was reported from: Fall River, 1; Springfield, 1; total, 2.

Trachoma was reported from: Boston, 1; total, 1.

Trichinosis was reported from: Cambridge, 1; Lakeville, 1; total, 2.

Typhoid fever was reported from: Bellingham, 1; Boston, 4; Gardner, 1; Waltham, 1; Worcester, 1; total, 8.

Typhus fever was reported from: Arlington, 1; total, 1.

Undulant fever was reported from: Boston, 1; total, 1.

Mumps continued to show a record high incidence for the seventh consecutive month.

Chicken pox, meningococcal meningitis, German measles, scarlet fever, typhoid fever and whooping cough were reported above the five year averages

Bacillary dysentery, diphtheria, measles, pulmonary tuberculosis, other forms of tuberculosis and undulant fever were reported below the five year averages

Lobar pneumonia showed a record low incidence for the second consecutive month

The focus for animal rabies that has been noted in the northeastern section of the State is still active in Middlesex County, cases having been reported from Burlington, Woburn, Danvers and Tewksbury

## REPORT OF MEETING

### NEW ENGLAND PATHOLOGICAL SOCIETY

A meeting of the New England Pathological Society was held on October 16, at the Boston Lying in Hospital Dr Earle B Clarke presided

The first paper, 'Morphologic Findings from Endometrial Biopsy from 100 Cases of Bleeding during the First Trimester of Pregnancy and from 34 Cases of Puerperal Pyrexia,' was presented by Dr Robert N Rutherford Application of the technic of endometrial biopsy to the problem of bleeding in the first trimester of pregnancy in 100 consecutive bleeding cases in the Out Patient Department of the Boston Lying in Hospital has evolved as a simple safe, quick procedure for the detection of the inevitability of abortion This is based on the high incidence of pathologic ova in which the embryo is absent or very defective and which form the bulk of spontaneous abortions in the first trimester The embryos in such specimens tend to die or cease developing, on an average six weeks before actual extrusion at the usual 'lamentable miscarriage' Fetal death or lack of fetal development initiates thrombosis, necrosis and hemorrhage within the decidua and beneath the placental plate, probably on the basis of slow withdrawal of the pregnancy corpus luteum hormone These changes are irreversible, and are easily recognizable as characteristic, even on frozen section Such a finding precludes any need for hormone treatment or restriction of the patient's activities, for Nature is rid of the uterus of defective human materials The procedure carries no danger to a normal pregnancy up to the fourteenth week Its diagnostic accuracy is very high in the 100 cases so studied, 50 were associated with pathologic ova, 42 with defective implantation or defective placental development and 2 with ectopic pregnancy, 6 patients were not pregnant Progesterone in massive doses was of no value in either major problem—defective fetal development or defective implantation, with or without placental or appendage fault

The technic has also been used to study the regeneration of the uterine mucosa following normal full term delivery and spontaneous abortion It has been demonstrated in 25 post partum cases that regeneration is complete within two or three weeks following delivery, that ovulation takes place about six weeks after delivery, but that lactation inhibits ovulation for varying periods Following spontaneous abortion, regeneration is complete in the ideal case in five to seven days, ovulation occurring fourteen days after a curetted abortion Failure to curette, or heavy preabortion progesterone therapy or retained placental fragments will not delay regeneration, but will delay resumption of the normal ovarian cycle Routine immediate postabortion curettage is recommended Subsequent impregnation can take place within two weeks

after abortion, and curettage is recommended as a time saving procedure in difficult sterility problems

In the discussion, Dr Somers H Sturgis stated that Dr Rutherford had shown that a biopsy of the lower uterine segment can be done without precipitating abortion It must be emphasized, however, that such a result cannot always reasonably be expected in less experienced hands The procedure certainly is never justified in the diagnosis of normal pregnancy Interpretation of the material is as significant as the method of taking the biopsy It would take a great deal of confidence for most physicians to empty a uterus on the frozen section findings without waiting for permanent sections However, it is possible to diagnose a nonviable fetus on frozen section of the decidua alone Dr Sturgis entirely agreed with Dr Rutherford's conclusions regarding the futility of progesterone treatment of bleeding cases by calling attention to the uselessness of giving this hormone to cases that already show irreversible, degenerative decidual changes He wondered, however, whether it might not be worth while to give 10 mg of this hormone as a routine, prior to taking the biopsy This might render the uterine muscle temporarily refractory and thus give a certain amount of protection to cases with an unaffected fetus Sometimes, a biopsy initiates uterine cramps, and if this protection were used, an occasional calamity might be averted

With respect to the second part of the paper on the regeneration of uterine mucosa following abortion and delivery Dr Sturgis stated that Dr Rutherford deserves a great deal of credit for his careful histologic examination of daily specimens of post partum endometrium So far as he knew, no such study had previously been performed to throw light on the state of the endometrium during regeneration after spontaneous abortion and after normal delivery in both lactating and nonlactating mothers A comparison of his results in these three groups reveals that endometrial regeneration after spontaneous abortion and curettage is complete in about one week, with evidence of ovulation by the fourteenth day and normal menses on the twenty eighth day Such an immediate return to the normal cycle is not unexpected It may be ascribed to an immediate release of the follicle stimulating hormone of the pituitary gland, previously inhibited by the high titer of estrogens produced by the products of conception A similar immediate release follows estrogen withdrawal under other circumstances For example, at the Massachusetts General Hospital, Dr Sturgis and his colleagues have inhibited the pituitary gland and suppressed the ovarian cycle for about three weeks in a large group of patients with dysmenorrhea It is notable that in these patients, as in women who have spontaneously aborted and who have been curetted, ovulation apparently occurs in about two weeks, and a normal period almost invariably about twenty-eight days after the estrogen has been abruptly withdrawn On the other hand, Dr Rutherford has noted that this prompt pituitary reactivation, with consequent ovulation, does not necessarily occur if curettage is not performed after spontaneous abortion In one of his cases, in which all the products of conception were identified so that no curetting was done, a biopsy on the thirty fifth day still showed regressing decidua The patient apparently had not ovulated Dr Sturgis was tempted to speculate on the possible role of retained decidua on the storage or metabolism of estrogen and its possible effect on the pituitary

In the other two groups of patients,—the nonlactating

and the lactating mothers,—Dr. Rutherford finds regeneration complete in about twelve days. This interval is what one might expect in comparison with that of seven days after abortions under three months. In the non-lactating mothers, as well as in some that lactate, ovulation did not occur in his cases for six weeks. The exact role of the lactogenic hormone in suppressing gonadotropic activity is not precisely known. Failure to lactate, however, does not necessarily indicate a subnormal production or absence of the lactogenic hormone. The trouble may lie in unresponsive breast tissue. It seems likely that production of lactogenic hormone post partum in some way represses the output of follicle-stimulating hormone for three to four weeks. If the mother does not or cannot nurse her child, the gonadotropic activity of the pituitary gland is released at that time, as evidenced by ovulation at about the fifth or sixth week in some cases. In many lactating mothers who continue nursing, however, the stimulus from suckling in some way continues the output of lactogenic hormone and the consequent repression of follicle-stimulating hormone. Dr. Sturgis considered the chief value, perhaps, of Dr. Rutherford's work to be in presenting clear evidence that, during the period of lactation amenorrhea, the endometrium is proliferative—in a relatively resting stage. Amenorrhea at this time, then, is associated neither with persistence of the corpus luteum of pregnancy nor with any new corpus luteum maintained by lactogenic hormone. A regenerated endometrium remains resting until the pituitary gland finally breaks through the inhibition of the estrogens of pregnancy and of the lactogenic hormone, and not till then does the normal four-week cycle of proliferation and secretion start.

The second paper, "Bilateral Cortical Necrosis of the Kidney: A report of two cases with some observations on the pathogenesis and evolution of the renal lesion," was presented by Dr. Walter H. Sheldon.

Two cases of symmetrical cortical necrosis of the kidney following toxic separation of the placenta were presented. The renal lesion consisted of necrosis in the wall of the afferent arteriole at the point where the vessel enters the glomerulus. This necrosis, which in most cases was associated with thrombosis and followed by retrograde extension in the intralobular and interlobular arteries, led to ischemic necrosis of the kidney. Similar lesions were found in the anterior lobe of the pituitary gland, in the pituitary stalk and in the tuber cinereum, as well as in the decum and adrenal gland.

Dr. Foster Kellogg, commenting on the clinical aspects of cortical necrosis of the kidneys, emphasized the difficulty in making the diagnosis clinically. He reviewed a series of cases with oliguria or anuria in association with toxemia of pregnancy or premature separation of the placenta, and concluded that if a patient with premature toxic separation fails to pass much urine in the first two or three days it does not signify definitely that she has cortical necrosis. It is perhaps better to force fluids and go on the assumption that she does not have cortical necrosis and may live, rather than to assume that she has cortical necrosis and is bound to die.

Dr. Richard Wadsworth stated that in a recent report he observed degenerative changes in the hypothalamus following sclerosis of the anterior lobe of the pituitary gland, in addition to lesions in the corpus callosum. He asked whether any degenerative cell changes were seen in either the optic or supraoptic nuclei of the hypothalamus, but Dr. Sheldon replied that he had looked specifically in these regions and found none.

Dr. Sheldon's remarks about the limits and distribution of the infarcted areas in the pituitary gland interest Dr. George Wislocki, who stated that the areas of infarction corresponded to the distribution of the superior hypophyseal arteries,—as investigated by him in the macaque monkey,—including the median eminence of the tuber cinereum, the pituitary stalk and the anterior lobe. The remainder of the tuber cinereum and the posterior lobe showed no infarction because, in Dr. Wislocki's opinion, their blood supplies derive from other sources, namely from hypothalamic branches independent of the pituitary gland, and from the inferior hypophyseal arteries. He suggested that when infarction of the stalk occurs, one should anticipate eventual damage to the hypothalamic hypophyseal tracts traversing the stalk, with related symptomatology.

The third paper, "Relation of Ovarian Stromal Hyperplasia and Thecoma of the Ovary to Endometrial Hyperplasia and Carcinoma," by Drs. George V. Smith, Le C. Johnson and Arthur T. Hertig, was read by Dr. Johnson. Changes occurring in nonfollicle-bearing, postmenopausal ovaries appear to be frequently associated with hyperplastic, bleeding endometria. These changes are characterized by masses of dense, well-vascularized stromal tissue in either the cortex or the medulla of the ovary, with a tendency to form whorls. Some of the stromal cells along capillaries in these whorls become large fat-containing polyhedral cells and look like cells of the theca interna. To these changes, the term "stromal hyperplasia" has been given. When large numbers of such cells form a nucleus, there tends to be some infiltration of lymphocytes and macrophages in the area, associated sometimes with cholesterol-like slits. At such times, foreign body giant cells surrounding the cholesterol slits mark their appearance. To these focal collections, the term "cortical granulomas" has been given. As both stromal hyperplasia and cortical granulomas pass the peak of the anatomic activity, collagen is laid down, and finally on a nest of whorled, hyalinized fibrous tissue remains. The almost constant association of these lesions with hyperplastic bleeding endometrium suggests that there may be a more than coincidental relation between the fat-cholesterol slits and estrogen production.

These changes are very similar to the whorling, vascularity, fat deposition and finally collagen deposition seen in thecomas, and in mixed theca-granulosa-cell tumors. There is also a close parallel between the polyhedral theca-interna-like cells in these lesions and similar cells in the theca-granulosa-cell group of tumors. Of such tumors seen at the Free Hospital for Women through 1935 as reviewed by Dr. Smith, 16 per cent were associated with carcinoma of the uterus. In a paper recently published, he observes that of 180 cases of postmenopausal carcinoma of the uterus during the same period, 87 per cent were associated with excessive amounts of ovarian stromal activity as judged by the quantity of whorled, vascular, stromal tissue, cortical granulomas and polyhedral theca-interna-like cells. This degree of stromal ovarian activity is much greater than that in a series of ovaries from prostatic patients over two years past the menopause who had had a normal menstrual history and no postmenopausal bleeding. Thus, there appears to be anatomic evidence of hyperestrinism in the ovary, in the form either of tumor or of evidence of increased stromal activity—in many cases of carcinoma of the uterus.

The discussion was opened by Dr. Smith, who stated that he was first impressed with hyperplasia of the stromal or thecal cell about six years ago, when combining the

pathological files of the Free Hospital for Women for granulosa cell tumors and cystadenofibromas. During this review, it became evident that the cystadenofibromas were associated with postmenopausal bleeding and endometrial proliferation, although of a degree not so marked as that in cases with granulosa-cell tumors. Until two years ago, however, thecal-cell hyperplasia was to him only an interesting observation. No correlation with other pelvic lesions was evident. At this time, he began reviewing pathology for a paper on cancer of the endometrium, and the frequency of thecal cell hyperplasia in cases with this type of cancer was immediately apparent. Eighty-seven per cent (156 cases) of the postmenopausal ovaries (180 cases) had what was interpreted as slight to marked thecal-cell activity. Sections of endometrium were available from 62 of this group, and 48, or 77 per cent, showed more or less proliferation, mostly less. Dr Smith was unable to correlate the amount of thecal cell hyperplasia with the amount of endometrial activity. Endometrial hyperplasia has for some years been considered a possible forerunner of later endometrial cancer. This idea received support from the findings by Dr Smith and others, of a relatively frequent association between granulosa-cell tumors and carcinoma of the endometrium. About one fifth of his patients with granulosa cell tumors after the menopause also had endometrial cancer. Conversely, of 180 postmenopausal patients with carcinoma of the endometrium seen before 1936 whose ovaries had been sectioned 5 or 27 per cent, had granulosa cell tumors. If he includes those with marked diffuse thecal-cell hyperplasia and those with cystadenofibroma, the percentage of cases of endometrial carcinoma with unmistakable microscopic ovarian activity becomes 8. Compared with the control group of postmenopausal ovaries from cases of prostatic carcinoma which Dr Johnson and he examined together, 90 per cent of the group with carcinoma of the endometrium had significant microscopic ovarian activity, ranging from slight thecal-cell hyperplasia to actual granulosa-cell tumor. He would be more excited about the former if the available sections of endometrium had shown more convincing evidence of estrogenic stimulation. Perhaps lesser grades of thecal-cell activity yield subthreshold amounts of estrogenic steroid for the endometrium. Perhaps, also, it is wrong to assume that thecal-cell activity indicates the production of only an estrogenic steroid. For the present, all that can be submitted is that based on microscopic study, cessation of menstruation does not necessarily mean that the ovaries have ceased functioning.

The last paper, "Observations on a Series of Early Normal and Abnormal Human Ova Obtained prior to the First Missed Menstrual Period," by Drs Arthur T. Hertig and John Rock, was presented by Dr Hertig. A series of eight early human ova,—four pathologic and four normal,—discovered incidentally in uteri removed surgically before the first missed menstrual period, was reported.

The ovulation age of the normal ova varies from eleven to sixteen days, and that of the pathologic ova from twelve to thirteen days. The normal specimens, including the youngest human ovum thus far observed, encompass the developmental period just before and just after the formation of the chorionic villi. The uteroplacental circulation has just begun and consists of a series of large anastomosing sinusoids developed from the endometrial capillaries whose finer branches are tapped directly by the eroding trophoblast thereby flooding the trophoblastic lacunae (future intervillous spaces). Hemorrhage into the surrounding endometrium is a constant feature in normal as well as in abnormal cases. Recent hemorrhage—villi-

ble in amount—is also free in the uterine cavity in both normal and abnormal cases, and arises from the defect in the endometrium created by the embedding ovum.

The significance of the pathologic ova lies in the fact that from them can be evaluated certain factors in the pathogenesis of spontaneous abortion. In all four of these specimens, the ovum itself is definitely defective, either because of lack of an embryo or because of some local or general defect in the trophoblastic development. Detailed studies are in progress to determine whether the environment of these ova is significantly different from that of the four normal ova and hence could have caused the ovular defect, or whether the latter is present at such an early stage of development in spite of a normal environment.

In the discussion, Dr Wislocki emphasized the importance of Dr Hertig's preparations, which, he believes, realize the hope of embryologists of discovering and studying the earliest stages of human development. Through the efforts of Drs Hertig and Rock, this goal is well on its way to being attained. Their series contains perfect implantation stages of the eleventh and twelfth days, and since the free blastocyst presumably attaches to the endometrium on the ninth day (as in the macaque), it is anticipated that this small but critical gap in the knowledge of implantation of the human egg will soon be filled.

## BOOK REVIEWS

*Diseases of the Thyroid Gland, Presenting the Experience of More Than Forty Years*. By Arthur E. Hertzler, MD. 4<sup>th</sup> cloth, with 354 illustrations, and 2 color plates. New York: Paul B. Hoeber, Incorporated, 1941. \$8.50.

In his preface, the author states that this book is "no wise a treatise on the thyroid gland. It is merely a record of his studies which now extend over a period of nearly fifty years."

The style is unorthodox but entertaining. The plan of the book, as set forth in the "Table of Contents," the system of classification of goiters, and the illustrations are excellent. The text is confused and confusing, repetitious and sometimes circular in reasoning. Many of the assertions made invite dispute—for example, "Of what the thyroid gland has to do once the body is developed we know less than nothing." It seems to the reviewer that at least something is known about the function of the thyroid gland in the adult organism.

The genesis of this book, the author says, was the criticism leveled by pathologists at his theory of the toxic nature of myxedema. It seems to the reviewer that a not very successful attempt to refute these critics is the chief purpose of this book.

There is much teleologic reasoning and argument by analogy with commonplace mechanisms. Total thyroidectomy is advocated for all goiters, and the claim that myxedema is relieved by such an operation is put forward. There is much discussion of physical changes in the colloid (based exclusively on staining reactions), which leads to disturbed cellular functions. A thesis is maintained for the existence of a degenerative state of the thyroid gland in addition to the "toxic" factor in the production of "goiter heart," a term that is used quite loosely throughout.

The author's plea to regard the basal metabolic rate as an adjunct in diagnosis rather than as an absolute expression of thyroid function is well taken, but is so distorted in its emphasis as to lead to a dangerous disregard of a



procedure that, when competently interpreted, has proved its utility in the general run of cases.

The sections on the surgical pathology of goiter emphasize the lack of uniformity of histologic states as correlated with the clinical picture; the importance of the stage of the disease is appreciated in this relation, and the fact that large cancers grow from small adenomas is reiterated.

The author lays great stress on the relief of such symptoms as tachycardia, nervousness and weight loss by the removal of nontoxic goiters, but he cites a case in which such symptoms were relieved by the removal of a large lipoma of the neck. This case throws some doubt on the relation between relief of these symptoms and thyroidectomy in his cases of nontoxic goiter.

*Health and the Doctors. In: Propaganda Analysis: A bulletin to help the intelligent citizen detect and analyze propaganda.* Vol. IV, Number 11. 4°, 16 pp. New York: Institute for Propaganda Analysis, Incorporated, 1941.

This issue in the series of pamphlets on propaganda analysis is concerned with the efforts of organized groups to influence the public in the type of medical care to be selected. The philosophies, propaganda methods and motives of the various groups are opposed and analyzed. The arguments of the organizations sponsoring outright socialization and state control are presented more favorably than those of any other, and one gains the impression that the editor, wittingly or unwittingly, has himself subtly expressed a viewpoint in support of socialized medicine. The pamphlet is worth reading by the critical student interested in this subject.

*Fatal Partners: War and disease.* By Ralph H. Major, M.D. 8°, cloth, 342 pp., with 13 illustrations. New York: Doubleday, Doran and Company, Incorporated, 1941. \$3.50.

War and disease have always gone hand in hand. Dr. Major has gone through the records of history and brought into the pages of a single volume the chief aspects of medical interest in relation to military combat. The story is an interesting one. Unfortunately, the style in which the book is written takes away from the pleasure of reading; there is evidence of haste in compilation. To the reviewer, the illustrations often seem to be of slight value, and the book cannot be highly recommended on this account. Although the author presents much that is of value, he has not eliminated considerable irrelevant material.

*Vitamin K.* By Hugh R. Butt, M.D., M.S. in Medicine, and Albert M. Snell, M.D., M.S. in Medicine. 8°, cloth, 172 pp., with 39 illustrations, and 14 tables. Philadelphia: W. B. Saunders Company, 1941. \$3.50.

The problems posed by the discovery of the existence and probable importance of vitamin K constituted a challenge that was met forcefully and adequately. This book represents the tremendous strides that can be made in modern research within the compass of a few years once the impetus has been given. As a result of this co-ordinated experimental and clinical research, practical results of great, lifesaving value have materialized. The first portion of the book is devoted to the historical aspects involving the initial studies in hemorrhagic disease of chicks. Then follows a discussion of the chemistry of vitamin K and, finally, of the clinical studies and applications. Conditions unassociated with vitamin K deficiency and hence not influenced by its use are also considered. This small volume

presents an excellent summary of a subject that should be familiar to all physicians. An excellent bibliography is appended.

*Pathology of the Oral Cavity.* By Lester R. Cahn, D.D.S. 8°, cloth, 240 pp., with 165 illustrations. Baltimore: The Williams and Wilkins Company, 1941. \$5.50.

Half of this work is devoted to a description of the pathology of the teeth and jaws, and the remainder to the common lesions involving the soft tissues of the oral cavity.

The book, as its title indicates, is truly a treatise on the pathology of the oral cavity and is especially useful in relating the pathologic tissue changes with the clinical findings in oral lesions.

There is an abundance of illustrations, a few of which are in color. The histopathological plates are especially clear, and the bibliography is brought up to date.

On the whole, the descriptive material is too brief to be regarded as a textbook, but the work can be recommended as a reference to the dental student, to the scientifically minded practitioner of dentistry, and to physicians interested in oral disease.

*Lymphatics, Lymph, and Lymphoid Tissue: Their physiological and clinical significance.* By Cecil K. Drink, M.D., D.Sc., and Joseph Mendel Yoffey, M.Sc., M.F.R.C.S. (Eng.). 8°, cloth, 406 pp., with 50 illustrations and 45 tables. Cambridge, Massachusetts: Harvard University Press, 1941. \$4.00.

The reviewer considers this a work of unique importance that collects material from varied sources to produce a comprehensive and valuable description of the present physiology of the lymphatic system. The authors have personally added a great deal to the knowledge of lymphatics and lymph, and are admirably qualified to produce this monograph, in which their own work and that of others are critically evaluated. They deserve particular commendation for carefully separating fact from speculation in the application of their material.

The book should be read by every physician desiring to keep abreast of significant advances in medicine. Although the biologist and teacher will be fascinated by the basic anatomy and physiology presented, the work should prove at least as interesting and valuable to the practitioner of medicine.

Wide applications of the knowledge of the lymphatic apparatus are presented. The hematologist, for example, will be interested in the discussions of the production and loss of lymphocytes, and the bacteriologist in the material on the transport of viruses by way of the lymphocytes; the internist and surgeon will both find valuable matter on edema and inflammation.

*Sulfanilamide and Related Compounds in General Practice.* By Wesley W. Spink, M.D. 8°, cloth, 256 pp. Chicago: The Year Book Publishers, Incorporated, 1941. \$3.00.

Since the introduction of the sulfonamides as a new chemotherapeutic approach to the treatment of infection a veritable flood of studies has appeared. This small volume endeavors to summarize the principal facts gleaned from the literature. Appropriate attention is directed to the untoward reactions that may be associated with various chemicals. The inclusion of sulfadiazine brings the book fairly well up to date. Those seeking a brief but adequate survey of the sulfonamides will profit from this book.

(Notices on page viii)

# The New England Journal of Medicine

Copyright 1943 by the Massachusetts Medical Society

VOLUME 226

MARCH 5, 1942

NUMBER 10

## EVALUATION OF REGIONAL LYMPH-NODE DISSECTION IN THE TREATMENT OF CARCINOMA\*

GRANTLEY W. TAYLOR, M.D.†

BOSTON

**D**ISSECTION of the regional lymph nodes is carried out as a routine procedure in carcinomas of the breast, the rectum, the colon and the stomach, as part of the radical operation for dealing with the primary carcinoma. Dissections are elective procedures in the treatment of carcinomas and melanomas of the skin, and of carcinomas of the lip, mouth, external genitalia and various other organs and regions. With the object of determining the indications and value of these elective dissections, over 5000 cases of neoplastic disease have been reviewed from the recent experiences at the Collis P. Huntington Memorial Hospital, the Massachusetts General Hospital and the Pondville Hospital.

### *Indications for Dissection*

It may be said at once that dissection is indicated when operable metastases are present. Unfortunately, this simple statement implies that the clinical recognition of the presence of metastases is accurate. However, metastases may be present before the regional nodes become obviously enlarged, and slight enlargements may have innocent causes in many cases. Enlargement of lymph nodes to a size greater than 1 cm. is strong evidence of metastasis, but there is still the possibility that the enlargement is due to inflammation rather than to metastasis. Actually, there is an error in the clinical recognition of lymph node metastases of 15 to 30 per cent, varying with the region involved, the obesity of the patient and the care and experience of the examiner.

Because of this clinical error, it is desirable to determine—from the characteristics and the usual course of the primary carcinoma—the likelihood of lymph node metastasis in a given case. For example, although carcinomas of the lip in general

metastasized in 24 per cent of the cases, it was observed that metastases occurred in only 7 per cent when the primary carcinoma was less than 1 cm. in greatest extent, and in only 6 per cent of the cases with carcinomas of low malignancy. Similar studies of various other cancers confirmed the opinion that the tendency to form metastases is associated with long duration, large size, high grades of malignancy, an invasive as opposed to a papillary type of growth and recurrences at the site of the primary cancer. In the absence of obvious lymph node involvement, it is only by evaluating these aspects of a cancer that one can arrive at an opinion concerning the presence of metastases.

### *Optimum Time of Dissection*

It may be stated at this point that dissection may reasonably be deferred until metastases can be detected. Thus, fewer unnecessary dissections will be performed. When dissection is deferred until the lymph nodes are obviously involved, however, it is probable that some patients with metastases will have lost their best chance for cure as a result of the delay, and that other cases may prove to be inoperable as a result of inadequate follow-up observations. No absolute rules can be laid down regarding prophylactic, as opposed to delayed, dissection. But, when a primary carcinoma is one with little likelihood of forming metastases, in a patient who is not in sufficiently good general condition to withstand operation and who can be depended on to report faithfully for observation, it is reasonable to adopt a policy of watchful waiting. On the other hand, when there is considerable likelihood of metastasis in a patient in good general condition who may find it difficult to report regularly, prophylactic dissection is favored.

It should be unnecessary to insist that cure of the primary carcinoma is a prerequisite to any

\*Presented at the annual meeting of the New England Surgical Society, November, New Hampshire, September 6, 1941.

†Instructor in surgery, Harvard Medical School; associate visiting surgeon, Mass. General Hospital; visiting surgeon, Pondville Hospital.

elective dissection. It is also a matter of experience that the mortality and complications following dissection are minimized if the dissection is postponed until after healing of the site of the primary carcinoma has taken place. Thus, the optimum time for performing a prophylactic dissection is two to four weeks after eradication of the primary carcinoma. When the lymph nodes are already involved at the time the patient is first seen, the interval may be shortened, but the dissection should still be deferred until after treatment of the primary carcinoma. When one follows a policy of watchful waiting, the patient should be examined at least at monthly intervals for a year after treatment of the primary carcinoma, and bimonthly during the second year. In these cases, dissection should be performed at once if involvement of the nodes is detected.

Extent of Dissection

The extent of a regional lymph-node dissection must be based on knowledge of the lymphatic drainage pathways from the area involved in the primary carcinoma, and the known behavior of the carcinoma concerning node metastases. For example, carcinomas of the lip and buccal mucosa rarely form metastases below the level of the omohyoid muscle, and dissections in these cases may therefore be limited to the upper neck. Carcinomas of the external genitalia may form primary metastases along the external iliac vessels as well as in the superficial nodes of the groin; it is probable that a greater number of cures would result in these cases if the radical Basset type of dissection, instead of a superficial inguinal dissection, were employed.

Bilateral dissections are frequently indicated in lesions involving the lip and the external genitalia. In lesions situated in an area of potential lymphatic drainage in more than one direction, such as the shoulder or flank, it may be necessary to carry out dissections of two areas, such as the neck and axilla, or the axilla and groin. Bilateral or multiple dissections should be performed in stages, rather than simultaneously.

Results

In the results obtained by dissection, only those cases are included in which lymph-node metastasis proved to be present. Untraced cases, and patients dying of intercurrent disease, are excluded as inconclusive. A further group is excluded in which failure resulted because of failure to control the primary carcinoma. In these cases, a dissection is obviously futile.

The results of dissection are presented in Table 1. Although these figures have no standing as an

end-result report, because of the exclusions mentioned above, they probably represent what may be accomplished by regional dissections in properly selected cases when metastases are present.

TABLE 1. Results in Cases of Cancer with Dissection of the Involved Regional Nodes.

PRIMARY TUMOR	NO OF CASES	CURES	
		NO OF CASES	PERCENT AGE
Skin	36	12	33
Melanoma	38	7	18
Lip	100	58	58
Tongue	21	9	43
Mouth (other parts)	33	14	42
Vulva	14	5	35
Scrotum	10	2	20
Penis	21	11	52

These results further emphasize the fact that a large number of failures are properly attributable to local recurrence or persistence of the primary carcinoma.

It has been suggested in some clinics that the results of dissection may be improved by the employment of preoperative or postoperative radiation therapy. Although some of the patients in the present group received such treatment, there was no thorough trial of the method. In general, it has been believed that preoperative treatment postpones and complicates the dissection, and that postoperative treatment is of no benefit after a proper block dissection.

Postoperative Mortality

The figures for postoperative mortality as a result of dissection cover all cases, that is, including the figures for those in which dissection revealed no lymph-node involvement and those in which there was eventual failure through a lack of control of the primary carcinoma. When one considered the mortality incident to axillary dissection, it seemed reasonable to include patients subjected to radical mastectomy. The mortality is shown in Table 2.

Detailed analysis indicates that many of these postoperative fatalities might have been avoided.

TABLE 2. Postoperative Mortality in Cases with Dissection.

REGION	NO OF CASES	DEATHS	
		NO.	PERCENT AGE
Upper neck	601	6	1.0
Neck (radical operation)	112	4	3.6
Jaw (resection)	58	5	9.0
Axilla	1224	29	2.4
Groin	260	10	3.8

One of the commonest errors consisted in operating on the primary focus of disease and the regional nodes at a single sitting. Many of the bilateral dissections were carried out in a single

operation. It is hoped that improvements in anesthesia and operative technique, the employment of chemotherapy in cases that develop infection and the performance of multiple operations in stages rather than simultaneously will contribute to a lowered mortality.

### SUMMARY AND CONCLUSIONS

A review of the results of dissection in over 5000 cases of neoplastic disease is presented.

The decision to carry out a regional lymph node dissection in a case of cancer depends on the presence or the likelihood of development of metastases. The extent of dissection depends on the known behavior of the cancer and the anatomy of the lymphatic drainage areas. Prophylactic dissections may be performed in extensive carcinomas of high malignancy, but dissection may be deferred when there is little likelihood of metastasis, provided that the patient can be followed carefully. Control of the primary carcinoma should precede any dissection.

Dissection is capable of curing metastases in a considerable number of cases, with a postoperative mortality rate that should not be excessively high.

264 Beacon Street

### DISCUSSION

DR ERNEST M. DALAND (Boston). Dr Taylor and I are in full accord on all the facts that he has presented. I shall simply emphasize one or two points.

If one postpones a regional dissection, one should keep a very close check on the patient. We have a general rule that these patients shall report every month for the first year, every two months for the second year, every three months for the third year and so on. In private practice one should be equally careful to see that the patients turn up and have their lymph nodes checked. For many lesions like those on the lips, it is perfectly satisfactory to wait.

I agree that lip and neck dissections, or any other type, should be done in two stages. I have given up the idea of doing a V lip and a neck dissection at the same time. The majority of the lymph nodes palpated in the neck at the time that the primary lesion is seen clear up as soon as one gets rid of the primary lesion and the wound heals. In other words, they are inflammatory. If the nodes persist after a few weeks, I think that one should go ahead and do the dissection.

I do believe that a prophylactic dissection should be done in cases of malignant melanoma, when it is possible to say to which nodes the tumor would be likely to metastasize, for example, in the malignant melanomas of the extremities. I encountered a malignant melanoma in the suprasternal notch a few years ago. It was not possible to do a regional resection, since it would have meant dissection of the mediastinum and both sides of the neck, and perhaps the axilla. If one is dealing with a melanoma of the extremities, and they are much commoner there, one should do a radical inguinal and saphenous dissection including the nodes along the iliac vessels, in the

upper extremity, one should do a radical dissection of the axilla.

Inasmuch as Dr Taylor's figures have proved that clinical observation is so very inadequate in revealing whether or not the lymph nodes are involved, one should not trust to palpation, but as soon as the primary lesion has been destroyed, one should go ahead with the prophylactic dissection, if necessary.

If Dr Taylor had not explained his figures as carefully as he did, we might have been deceived by the relative values of neck dissections on lips and tongues. In the table he showed, 58 per cent of the cases with cancer of the lip and positive nodes were cured whereas in cancer of the tongue, 43 per cent were cured. Of course, that does not represent the relative morbidity or mortality in these two types of cancer. In the former, we operate on most of the cases unless there is very deep fixation. In the latter, we tickle really very few of them, since we must wait for the primary lesion to be destroyed. Because we fail in curing the primary lesion in many cases, and because the nodes when we do feel them are so far advanced, we do relatively few neck dissections. Curability of cancer of the tongue is consequently far below that of the lip.

If one does no more than cure a third to a quarter, as Dr Taylor said in his final remarks, I believe that one will have accomplished something. If these cases were seen earlier, the number of cures for metastatic nodes would be raised considerably.

DR ERNEST L. HUNT (Worcester, Massachusetts). At the risk of being accused of reactionism, I want to point out that my discussion deals wholly with the surgical approach and not the radiation approach.

Dr Taylor has rendered a real service in conducting a research that turns the light of experience on the difficult problem of when and to what extent block dissections should be used to head off the extension of malignant growths, and for so concisely stating his findings and conclusions for our guidance.

In our individual experiences, I am sure that we have all made dissections and found the lymph nodes to show microscopical evidence of inflammatory process only. I am equally sure that we have deferred dissection and later had occasion to regret it.

Given a primary lesion with secondary nodes, those which seem inflammatory may harbor cancer, and those which seem cancerous may prove only inflammatory. Hence, I incline to the belief that one should consider persistence of more importance than size, and act on the principle that failure of nodes to disappear entirely within four weeks after removal of a primary focus implies malignancy. Assuming that to be so, one may well ask, is it logical to await the resumption of activity, as manifested by increase in size of the nodes, before taking preventive action? It must also be admitted that quite sizable nodes may escape detection, even by well trained fingers. To be sure, it is comforting to believe that secondary nodes can probably be advantageously removed even when they have attained a diameter of 1.0 cm., but is one justified in waiting for so insidious a process to attain that much momentum before acting to head it off?

Dr Taylor does not mislead us regarding this difficulty, because he points out the 15 to 20 per cent error in recognition of lymph node involvement. To meet that discrepancy, he directs attention to the size and grade of malignancy of the original growth. Although I am in general agreement with the precepts he defines, I wish, nevertheless, to stress the fact that a policy of watchful

waiting entails many circumstantial pitfalls that may be avoided by prophylactic dissection.

Such a pitfall is illustrated by the case of a seventy-two-year-old retired business man who regards himself as a diabetic, tests his urine frequently and is meticulous in diet. Two years ago, he left for Florida in October, conscious of a "cold sore" on his lip, about which he did not think it worth while to invite his physician's opinion, although he was careful to have his urine and blood sugar tested. He returned in May, with an ulcer on the left side of his lip and a surrounding zone of induration about 8 mm. in diameter. No lymph nodes were definitely palpable, although I thought I could feel a tiny nodule less than a rice grain in size, in the submental angle close to the jaw bone. A liberal wedge excision was done, and an excellent cosmetic result obtained. The pathological report was squamous-cell epithelioma of low malignancy. On the eve of his next departure to Florida, in October, 1940, the submental nodule could not be felt, and the lip was perfectly healed. On his return in May, a sizable node was palpable under the angle of the jaw, on the left side, and the submental nodule was definitely palpable. A suprahyoid dissection of the middle and left sides of the neck was done on May 26, 1941. The pathological report was: "Metastatic squamous-cell epithelioma of low malignancy; normal salivary gland."

Here was a very careful man, under the obsession that he was a diabetic, who, in both the primary and secondary episodes, sacrificed valuable time in relation to a lesion that threatened his life, for the sake of a sojourn in Florida to benefit his general health and diabetic tendency. Certainly, one may assume that a prophylactic dissection after the first operation would have been of greater value to him than one done a year later after the growth had become well implanted and actively growing in a node far around under the angle of the jaw.

If removal of regional nodes is accepted as obligatory in cancer of the breast, does not the same principle apply to the lip or vulva, allowing of course for the infection inherent in the situation of the orificial growths?

Considering the nature of cancer, I wonder if we do not rely too naïvely on this matter of grading. I have been asking myself the questions: Does the degree of malignancy depend entirely on the histologic structure of the growth? May not a growth acquire a higher degree of malignancy according to environmental factors, such as persistent irritation, infection, diet and perhaps hereditary factors of susceptibility and immunity? In the case cited above, a growth of low malignancy histologically had a lively invasive quality.

I conclude by voicing the following convictions: When in doubt whether a prophylactic dissection is indicated, and in the absence of serious contraindications, the correct principle is to err on the side of thoroughness and do the dissection as soon as it may be done safely, rather than to be driven to it at some future and less favorable moment.

Too great reliance should not be placed on grading in justification of a negative attitude toward preventive surgical treatment.

DR. DAVID W. PARKER (Manchester, New Hampshire): I agree entirely with Dr. Taylor's conclusions. I therefore do not wish to take up time with discussion, but should like to report briefly a case of squamous-cell carcinoma in a thirteen-year-old boy, which, I think, is worthy of record.

I saw this child for the first time a few days prior to July 15, 1941. A small nodule or papule had appeared on the inner surface of the upper third of the right arm

three or four months previously. He thought that it was probably an infection, and squeezed it. It did not disappear, however, but grew progressively larger. In the middle of June, he consulted a doctor, who thought it was a cyst and opened it. He expressed some bloody fluid, but a sinus persisted and did not heal. There was no pain, but there was localized redness and thickening. On July 15, I excised the nodule and sent it to Dr. Ralph Miller, in Hanover, for examination. The pathological report was as follows:

The specimen consists of a partially formalin-fixed gray-white red-brown, roughened piece of skin, 1.0 by 0.8 cm., covering a flattened gray-brown and red-brown piece of tissue, 0.8 by 0.7 by 0.3 cm., which, on section, reveals a cavity 0.5 by 0.8 by 0.2 cm., filled with soft, dark, brown-red material. Microscopical examination reveals anaplastic squamous epithelial cells lying beneath normal stratified squamous epithelium, with clear cytoplasm, in which are many areas of hemorrhage. Pathological diagnosis: squamous-cell carcinoma (Grade II).

I was unable to find any palpable nodes in the axilla. However, because a definite percentage of involved axillary nodes are not palpable, — a point that has been brought out so effectively in Dr. Taylor's paper, — excision of the axillary contents seemed advisable. This was done on July 24. The pathological report was as follows:

Examination reveals normal lymph nodes. There is no evidence of malignancy. In view of the low degree of malignancy of the original tumor, and the absence of any evidence of it in the surrounding tissue, the prognosis is excellent.

In this case, there was no involvement of the axillary contents, yet I am firmly convinced that the procedure was definitely justified, and should be carried out as a matter of routine in lesions of this type.

DR. TAYLOR (closing): I was afraid that I should upset certain of the orthodox brethren by not coming out more strongly for prophylactic dissection, and I am very grateful to Dr. Hunt for making the point that, if one is in doubt, dissection should be performed. I did not emphasize enough, perhaps, the absolute necessity for control of the patient, if any deferred program is contemplated and dissection is not offered as part of the initial treatment. The difficulty with Dr. Hunt's patient who went off to Florida is the same thing in a higher economic bracket that we see in the clinic when a patient comes to Boston from the outposts of civilization; once he gets back there after the carcinoma is treated, one knows perfectly well that he will never come out of the woods again until he has a massive recurrence. Dr. Hunt's patient would not come off the beach until he had a massive recurrence.

The patient who cannot be controlled and seen at frequent intervals should have the benefit of a prompt regional dissection. How much damage is done by deferring the dissection and waiting until the nodes appear, I cannot say. I tried to determine that in relation to cancers of the lip. Only 33 per cent of the patients in whom the dissection was deferred for longer than six months from the time the lip was operated on were cured, in contrast to those in whom the dissection was done at once, in whom, even in the presence of positive nodes, the cure rate was about 60 per cent.

I think that the group deferred for more than six months contained a good many neglected cases or cases in which the best program was not followed. There may be an optimum time when, even with deferred dissection,

provided the operation is done promptly on the appearance of the nodes, the patient's chance of cure is not jeopardized to a severe degree

The question has been raised whether cancer can be in transit from the primary focus to the regional nodes and, if so, how long it will take to complete its course so that it will all have arrived at the nodes by the time dissection is performed. One of the theories of dispersion of cancer along the lymphatics is the so-called 'permeation theory' early expounded by Dr Sampson Handley, which is the basis for block dissection in cancer of the breast, the ambition being to remove all the intervening lymphatics

There has been a tremendous amount of work and observation concerning the usual method of dispersion of cancer along the lymphatics, it is usually by embolism of carcinomatous fragments in the lymph stream. Cancer cells probably move as promptly as the lymph stream moves, to the regional nodes—the first point at which they are arrested. That means, I suppose, that the maxi-

mum period of transition is measured in hours rather than in longer intervals. However, a number of cancers, notably the melanomas, permeate the lymphatics. We have all seen the blueberry muffin appearance surrounding the primary focus of an excised melanoma, which means that permeation is in progress. Pack of the Memorial Hospital, in New York City, stated that it takes about two weeks for melanomas to travel up the lymphatics to the regional nodes, therefore, one should wait two weeks before doing a regional dissection. I am embarrassed to say that I do not know whether that is true or not.

Ewing has pointed out that cancer of the penis frequently spreads by way of permeation and that is the reason for the proposed radical block dissections, in one stage, of both groins and the primary cancer. This procedure is theoretically ideal, but almost lethal, in that the mortality is so high as to be justified with difficulty. I furthermore, cure of cancer of the penis may be achieved by operation on the penis and, after an interval, dissection of the groins, by separate operations.

## THE USE OF STILBESTROL IN THE RELIEF OF ESSENTIAL DYSMENORRHEA\*

SOMERS H. STURGIS, M.D.†

BOSTON

IN a previous paper,<sup>1</sup> it was pointed out that relief from cramps in so-called "essential dysmenorrhea" could be consistently obtained by treatment with estradiol benzoate. The present paper presents an analysis of comparable results with Stilbestrol by mouth in the same group of patients that responded previously to estradiol given subcutaneously.

Considerable evidence in the recent literature is now available to prove that Stilbestrol is a highly potent preparation. This synthetic substance, administered orally, has been shown to have the same effect as natural estrogens in controlling the symptoms of the menopause,<sup>2</sup> in producing a proliferation of the endometrium and causing "estrogen withdrawal" bleeding after cessation of treatment,<sup>3</sup> in converting the castrate type of vaginal smear into the "estrous" type,<sup>4</sup> and in inducing growth and swelling of the breasts.<sup>5</sup> The convenience of oral therapy, together with the fact that Stilbestrol is many times more potent than any oral preparation of a natural estrogen, prompted me to determine whether it could be used effectively to control the cramps of essential dysmenorrhea.

It must be emphasized that a satisfactory response to estradiol benzoate could be consistently obtained only when such a course was started early enough in the monthly cycle.<sup>1</sup> In a patient with approximately twenty-eight day

cycles, the first injections were given within the first week at least twenty-one days before the expected menses. When endometrial biopsies were taken after estrin therapy that was timed in this way, the absence of a secretory endometrium in these biopsies was considered evidence that ovulation had been suppressed that month. The painless bleeding that followed such treatment was considered to be due to estrin withdrawal. In succeeding months, if no more treatment was given, the cramps inevitably returned. Such suppression of ovulation by estrin was regarded as a secondary effect, the primary effect in these cases being an inhibition of the follicle stimulating hormone of the anterior portion of the pituitary gland. The follicle normally matures and then ovulates about fourteen days before menstruation. This maturation can be prevented only by blocking follicle stimulation at least seven days previously, or twenty-one days before expected menstruation. When estrin treatment was started too late (that is, less than seven days before ovulation or twenty-one days before menses), the follicle matured, ovulation occurred (as demonstrated by a secretory endometrium) and the menses were accompanied by cramps. On this basis, therefore, it may be postulated that the growing follicle is dependent on the production of follicle stimulating hormone normally from about the twenty-eighth to the twenty-first day before menstruation. During this period, treatment with a potent estrogen will inhibit follicle stimulating hormone production and thus delay or suppress ovulation. From the twenty-first to the fourteenth day, however, the follicle appears to be independent of further pituitary stimulation, during this week, an equal dose of estrin cannot prevent progressive follicular development, maturation and ovulation.

The dramatic and complete relief from cramps during the first flow after cessation of a course of estradiol benzoate injections constitutes an ex-

\*From the Ovarian Dysfunction Clinic, Massachusetts General Hospital  
†Assistant Physician, Massachusetts General Hospital

cellent yardstick whereby these young women can evaluate the effectiveness of other therapy.

### METHODS

A group of consecutive patients who complained of disabling cramps every month but showed no organic pelvic disease has been under study in the Ovarian Dysfunction Clinic of the Massachusetts General Hospital for the last four years.

Nineteen patients, all but 1 of whom were under thirty years of age, received both a "control" series of injections of estradiol benzoate and one or more courses of Stilbestrol by mouth. In this analysis of the Stilbestrol courses, the result was considered satisfactory only when the patients were equally free from any cramps in the month that treatment was given. When mild cramps were present, or the pain was said to be "better" but not entirely absent, such a course of Stilbestrol was rated as unsatisfactory.

### RESULTS

Each patient received one course of injections of estradiol benzoate according to the specifications previously established<sup>1</sup> that completely eliminate cramps for one month.\* In each case, the control series satisfactorily eliminated pain during the next flow.

The oral dose of Stilbestrol† was 1 or 2 mg. daily for varying lengths of time, in an attempt to establish the minimum total dosage that would yield consistently satisfactory results.

The 19 patients studied received seventy-nine courses of oral treatment, and cramps were satisfactorily eliminated fifty-nine times. In the remaining twenty courses, pain was present during the flow that occurred immediately after treatment. This therapy, therefore, was satisfactory in preventing pain in 74 per cent of the trials. This figure does not, however, give a true indication of the effectiveness of the drug. In the discussion below, it is pointed out that the failures were caused by misapplication rather than by inefficacy of the medication.

The daily dose of 1 mg., occasionally 2 mg., of Stilbestrol was continued for from ten to twenty-four days. Of the fifty-nine times that such therapy satisfactorily prevented the cramps associated with ovulation, it was continued long enough to be followed by withdrawal bleeding forty-five times. The remaining fourteen courses, or 24 per cent, in the satisfactory group were followed not by a painless flow, but by approximately four

weeks of amenorrhea, concluding in characteristic, crampy menses. This occurred twelve times when the total dosage was from 10 to 17 mg., and only twice on a total dosage of more than 18 mg.

Six injections of 1.66 mg. of estradiol benzoate, totaling 10 mg. in all, was previously established as the amount necessary to cause withdrawal bleeding, and the same effect in the same group could be obtained consistently with approximately 20 mg. of Stilbestrol orally. A rough comparison of the stimulating effect of these two estrogens on the endometrium is thus obtained.

### TOXIC SYMPTOMS

Careful blood studies and liver-function tests after Stilbestrol treatment have been reported elsewhere.<sup>6,7</sup> The majority of these have failed to show physiologic cause for the commonest untoward symptom—nausea or vomiting. Thirteen of the 19 patients in the group under study admitted that they occasionally had mild to moderately severe abdominal distress during treatment, and 5 of these, or 26 per cent of the group, had nausea and vomiting sufficiently severe to make it seem advisable to discontinue therapy.

One patient had headaches during the concluding days of each course of Stilbestrol. Another complained of mental depression. One patient, during a fourth consecutive course of therapy, developed vaginal staining apparently caused by a 2-mm. pedunculated endocervical polyp that presented at the external os. Since previous examinations had failed to show such a polyp and since no similar episode of spotting had previously occurred, it was considered probable that the almost consecutive estrogenic stimulation over four months in this patient might have produced the growth.

### DISCUSSION

#### *Analysis of Failures*

The twenty failures occurred in 11 different patients. Since the doses used were similar to those in the satisfactory courses of treatment, these failures were not due to inadequate dosage. However, in seventeen of these twenty courses, treatment was started too late in the cycle to prevent the impending ovulation, as shown by the fact that the menses occurred less than three weeks after the start of treatment in each. In other words, Stilbestrol was started less than twenty-one days preceding menstruation and less than seven days preceding ovulation in these cases; at such a time, the dose used could not be expected to check the development of the follicle already under way.

\*This dose has been the same for every case in the present series: 1.66 mg. of estradiol benzoate (Progynon B) subcutaneously for six doses starting on the sixth day after onset of flow, and repeated every third day.

†Supplied through the kindness of E. R. Squibb and Sons, New York City.

The three remaining courses that failed were started more than twenty-one days before the next menses. The failure of one course, started twenty-two days before a period, emphasizes the difficulty of any attempt to establish an arbitrary time limit (such as twenty-one days) for a given medication to produce a biologic effect in a group of different patients under variable conditions. The other two courses are diagrammed in Figure 1. Treatment

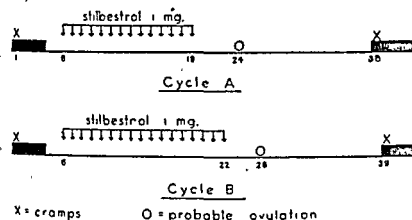


FIGURE 1. Case D. B.

Six previous cycles, while under observation without treatment, ranged from twenty-seven to thirty-one days in length. One mg. of Stilbestrol daily by mouth was started on the sixth day of the two above cycles. Treatment was continued for fourteen days in A and seventeen days in B. Menses with cramps occurred on the thirty-eighth day in A and on the thirty-ninth day in B. Cause of failure: Medication was started early enough to delay follicle development, but after conclusion of treatment, ovulation must have occurred (O on chart) to explain painful periods nineteen and seventeen days later. In this case, a dose of 2 mg. daily probably would have been sufficient to suppress completely the developing follicle and to prevent, rather than delay, ovulation.

was started thirty-three and thirty-four days, respectively, before the next periods occurred; it is believed that, in these cases, ovulation was delayed, but not prevented, by the medication given.

#### Calculation of Correct Timing of Treatment

In every patient, some variation in cycle length over a number of months is always present. This variation is probably related to the phase of follicle ripening, whereas the luteal phase of about two weeks appears to be the more consistent half of the cycle. Thus, in a cycle of thirty days, ovulation probably occurred two days late, and in one of twenty-five days, ovulation probably occurred three days early. It is on this basis that the so-called "rhythm theory" of conception control is worked out. To avoid intercourse at the time of ovulation, a patient must know from a record of previous cycles the earliest date that ovulation might occur, as well as the latest. A mass of clinical data in which cycle lengths and periods of abstinence have been carefully recorded bears out

in the main the theory of the constancy of the luteal phase of the cycle.<sup>8-10</sup> If one bears this in mind, it is clear that if ovulation is to be prevented by treatment that must be started one week previously, one must take into account the possibility of an early ovulation as demonstrated by previous short cycles. Thus, if a patient has a record of the occurrence of a cycle of twenty-five days, treatment must be started three weeks before this, by the fourth day after onset of the menses.

In the present series, medication was arbitrarily started the sixth to the eighth day after onset of the menses in each case. A later analysis of recorded cycle lengths in the 11 patients who had one or more failures brings out the fallacy of starting treatment according to any arbitrarily determined number of days after onset of flow. In each case, the shortest recorded interval while the patient was under observation before treatment has been counted. The possibility of the recurrence of a similarly short interval should have been considered in planning therapy. The importance of this, however, was not realized at the time. Seventeen times in these patients, a short

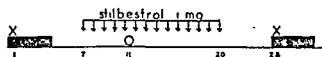


FIGURE 2. Case V. F.

Eight previous cycles, while under observation without treatment, ranged from twenty-five to thirty-one days in length. One mg. of Stilbestrol daily by mouth was started on the seventh day of the cycle and continued for two weeks. A period with cramps began on the twenty-fifth day of the cycle. Cause of failure: Ovulation probably occurred on the eleventh day (O on chart). Treatment started on the seventh day was too late to prevent this. With a record of a previous "short" cycle of twenty-five days, treatment should have been started at least one week before such an early ovulation, on the fourth day of the cycle.

cycle was already under way by the time that treatment was started on the sixth to the eighth day of the month. These failures could have been avoided by proper use of the available data.

To obtain suppression of ovulation with estrin consistently in any group of new patients, therefore, a careful record of at least eight consecutive cycles is indicated, just as a similar record is necessary in the calculation of the rhythm method of contraception.

When such a record is not available, treatment may be started on the first or second day of the cycle, to preclude the possible occurrence of the occasional, sporadic short cycle. Occasional occurrences of either



are responsible for the failures in even the most carefully planned rhythm schedules.

Figures 2 and 3 illustrate two of the failures, to emphasize the considerations given above.

### *Estrin-Withdrawal Bleeding*

In the clinical management of these young women, it is appropriate to know the minimum dose of an estrogen that will consistently produce a subjectively normal cycle. This might

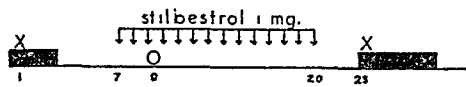


FIGURE 3. Case C. E.

Three previous cycles, while under observation without treatment, ranged from twenty-seven to twenty-nine days in length. One mg. of Stilbestrol daily by mouth was started on the seventh day of the cycle and continued for two weeks. A period with cramps began on the twenty-third day of the cycle. Cause of failure: Ovulation probably occurred on the ninth day (O on chart). Treatment to prevent this should have been started at least one week before such an early ovulation, on the second day of the cycle. In this case, the observation period of only three months was inadequate. Occasionally, a short interval such as this may occur without obvious cause, to upset the calculations based on normally regular cycles.

be defined as the occurrence of a painless flow after approximately a twenty-eight-day interval, and therefore involves two distinct estrogenic effects: estrin must be started early enough to prevent ovulation and the cramps with which it is associated; and estrin must be continued long enough to cause endometrial proliferation sufficient to break down into withdrawal bleeding when medication is stopped.

In the present study, approximately 20 mg. of oral Stilbestrol was established as a dose clinically comparable to six injections of 1.66 mg. of estradiol benzoate, totaling 10 mg. with regard to endometrial stimulation over a three weeks' interval followed by withdrawal bleeding about one week later. It is pertinent to inquire whether the interval from the last dose to withdrawal bleeding is characteristic of the amount of estrogenic stimulation, irrespective of the form of medication, or of the type of estrogen used. This withdrawal interval in the present series shows a variability that can be related essentially to differences in individual response to stimulation. Thus, the average interval before bleeding, after six routine estradiol injections, was seven to nine days. Yet in one patient it was after five, six, six, four and six days, and in another it was after nine, nine, eight, ten, eight and nine days. The limits for

withdrawal bleeding after estradiol were from four to ten days. Roughly, the same range, with similar individual differences, held true for the comparable oral doses of Stilbestrol. The limits were from four to nine days, the usual interval being from five to eight days.

### *Clinical Value of Estrin Treatment for Dysmenorrhea*

After four years' experience with intermittent estrin treatment for essential dysmenorrhea, it can be concluded that this type of therapy offers little as a method of permanent cure. During this time, a few patients received at least six to eight months of estrin treatment a year, yet almost all complained of the same disabling cramps, if no estrin was given, as they had before treatment was started. Only 2 patients have distinctly less severe cramps now, if not treated, than before estrin was given. Even this improvement over the course of two or three years may have little relation to hormone therapy, since many young girls spontaneously improve through a similar interval with no treatment at all. Clinical justification for estrogenic medication apparently does not lie in the promise of a cure for cramps.

One might reasonably question whether artificially induced anovulatory flows might not eventually cause permanent damage to the pituitary gland or the ovaries. No patient has been followed for more than four years, and this, of course, is too short a time to make possible a categorical answer. However, one of the striking results of this therapy is the invariable recurrence of characteristic dysmenorrhea when no treatment is given. Indeed, the very fact that 17 of the 19 patients in this series still have their typical cramps when untreated, even following a number of courses of estrin, argues against any permanent effect on the menstrual cycle. Assurance that no permanent harm is done can be found in the conclusions that relief after estrin is temporary and that administration of the drug does not constitute a method of cure.

It may be objected that it is not a sound gynecologic principle to upset regular ovarian cycles in an apparently normal person, even to the extent of a temporary suppression of ovulation. But these patients came to the clinic because of intractable monthly pain. I believe that the regular recurrence of a disabling complaint, no matter how normal the physiologic process with which it may be associated, justifies an attempt at relief.

It is well to emphasize once more the fact that relief from characteristic cramps after estrin when given according to the specifications outlined above is an all-or-none affair. Although partial mitiga-

tion of the pain may often be obtained by giving estrin as well as many other medicines directly before a period, complete absence of cramps is obtained with estrin only when ovulation is suppressed. It has been suggested that essential dysmenorrhea may be defined as menstrual cramps associated with the presence of a secretory endometrium. Differential diagnosis between this and other causes of recurrent abdominal pain can be derived from a test course of estrin therapy. The pain due to essential dysmenorrhea alone can be consistently and completely eliminated by this treatment.

Clinically, the main justification for estrin therapy in young girls with disabling dysmenorrhea straddles the psychologic and the economic aspects of this complaint. The reason that a patient consults a doctor in the first place is that she has been unable adequately to adjust her life to the certain expectancy of one to three days of disabling pain each month. In some cases, this results in a fixation of fear associated with menses, a psychologic complex that may take the form of futile opposition to all phases of life pertaining to the female sex. More frequently, these girls seem to show an immature personality, one that is irrevocably tied to the mother, the source of sympathy and the refuge against facing life during the monthly pain. The psychologic factor in dysmenorrhea so often mentioned in the literature is likely to be the result rather than the cause of the pain. To obtain the confidence of these girls, as well as to give them back some confidence in themselves, a guarantee of a menses free from pain may be the first step toward a better adjustment. Without such confidence, all the general measures that have been found helpful in the past—diet, exercises, routine habits and so on—are likely to be of no avail.

Some young women have been unwilling to take a position with the embarrassing but inadmissible knowledge that they will be inevitably forced to demand a few days' time off each month. Others, while at school, have found their work seriously interrupted by dysmenorrhea. One patient, a college student, had planned her wedding for the day after her graduation. It became clear from the previous regularity of her cycles that she also could confidently predict the onset of two days of completely disabling cramps for these very days. Estrin injections were advised and given. She was able to look forward to her plans free from anxiety. The important catamenia came and went free from cramps. The best chance for a permanent and complete cure of essential dys-

menorrhea appears to lie either in the normal pelvic changes resulting from pregnancy or in some type of surgical procedure. Either solution may have to be postponed for any number of reasons in any given case for six months, one or two years, or indefinitely. It is my belief that estrin therapy is justified as a temporizing measure in many of these cases, and that a patient can safely be offered relief for two months out of every three, for eight months out of each year, for a definitely limited time. The possibility of carcinogenic action contraindicates continuing such therapy indefinitely.

The cost of the natural estrogen in doses sufficiently potent to suppress ovulation is often prohibitive for many of these patients. Stilbestrol is poorly tolerated by about 1 in every 4 patients, but for those who show no untoward signs of sensitivity, the convenience of an effective oral preparation and its low cost appear to make it a valuable adjunct in the treatment of essential dysmenorrhea.

#### CONCLUSIONS

In a patient with essential dysmenorrhea, absence of cramps can be produced as effectively with Stilbestrol as with estradiol benzoate.

A daily dose of 1 mg. of Stilbestrol by mouth for twenty days produced a comparable effect to that produced by six injections of 1.66 mg. of estradiol benzoate, when given according to certain specifications.

To obtain this result consistently, the start of the treatment should be calculated from an accurate record of at least eight consecutive cycles. In a given month, medication should be started at least three weeks before the possible onset of the shortest previously recorded cycle length for that patient.

This therapy primarily inhibits the follicle-stimulating-hormone fraction of the pituitary gland and secondarily suppresses the growth of ovarian follicles, and hence ovulation during the time that treatment is given.

After conclusion of a course of treatment, the normal pituitary ovarian cycle is re-established, with the invariable recurrence in about one month, if no more estrin is given, of typical dysmenorrhea.

In 20 per cent of the patients, treatment must be discontinued because of gastrointestinal complaints.

Estrin therapy for essential dysmenorrhea is of value as a temporary, rather than a permanent, form of relief.

270 Commonwealth Avenue

## REFERENCES

1. Sturgis, S. H., and Albright, F. Mechanism of estrin therapy in the relief of dysmenorrhea. *Endocrinology* 26:68-72, 1940.
2. von Haam, E., Hammel, M. A., Rardin, T. E., and Schoene, R. H. Clinical studies on stilbestrol. *J. A. M. A.* 115:2266-2271, 1940.
3. Bishop, P. M. F., Boycott, M., and Zuckerman, S. The oestrogenic properties of "stilboestrol" (diethyl-stilboestrol). *Lancet* 1:5-11, 1939.
4. Shorr, E., Robinson, F. H., and Papanicolaou, G. N. A clinical study of the synthetic estrogen stilbestrol. *J. A. M. A.* 113:2312-2318, 1939.
5. Dunn, C. W. Stilbestrol-induced gynecomastia in the male. *J. A. M. A.* 115:2263, 1940.
6. MacBryde, C. M., Freedman, H., Loeffel, E., and Castrodale, D. The synthetic estrogen stilbestrol: clinical and experimental studies. *J. A. M. A.* 115:440-443, 1940.
7. Freed, S. C., Rosenbaum, E. E., and Soskin, S. Alleged hepatotoxic action of stilbestrol. *J. A. M. A.* 115:2264-2266, 1940.
8. Miller, A. G., Schulz, C. H., and Anderson, D. W. Conception period in normal adult women. *Surg., Gynec. & Obst.* 56:1020-1025, 1933.
9. Latz, L. J. Natural conception control. *J. A. M. A.* 105:1241-1246, 1935.
10. Fleck, S., Snedeker, E. F., and Rock, J. The contraceptive safe period. *New Eng. J. Med.* 223:1005-1009, 1940.

## PYRUVIC ACID STUDIES IN THE PERIPHERAL NEUROPATHY OF ALCOHOL ADDICTS\*

HERMAN WORTIS, M.D.,† ERNEST BUEDING, M.D.,‡ AND NORMAN JOLLIFFE, M.D.§

NEW YORK CITY

PERIPHERAL neuropathy in the alcohol addict is now generally considered to be the result of a nutritional deficiency and more particularly to be related to a deficiency of thiamin.<sup>1</sup> Experimentally, however, peripheral neuropathy in animals has been produced not only with thiamin-deficient diets,<sup>2</sup> but also with diets deficient in vitamin A<sup>3</sup> and riboflavin.<sup>4</sup> The problem is further complicated by the fact that Kolb and his co-workers<sup>5</sup> have recently been able to produce peripheral neuropathy in pigs fed on a diet containing adequate amounts of thiamin, but deficient in various other members of the vitamin B complex.

It is known that the diphosphoric ester of thiamin (thiamin pyrophosphate) is necessary for the proper catabolism of pyruvic acid,<sup>6</sup> and one would therefore expect hyperpyruvemia in thiamin-deficient subjects. In Oriental beriberi, a disease known to include thiamin deficiency, pyruvic acid does accumulate in the body fluids.<sup>7</sup>

Pyruvic acid is a keto acid and therefore a bisulfite-binding substance. Previous investigators<sup>8-10</sup> have frequently used the measurement of the total bisulfite-binding substances to determine the pyruvic acid level of the blood. More recent work<sup>11-14</sup> indicates that this is not justified and that a more specific method for pyruvic acid must be used.

We<sup>15</sup> have previously determined the concentration of pyruvic acid in the blood of 60 normal subjects. The figures varied from 0.77 to 1.16

mg. per 100 cc., the average being 0.98 mg. Blood pyruvic acid levels above 1.30 mg. per 100 cc. are considered abnormally high. The spinal-fluid pyruvate is 70 to 120 per cent of a corresponding blood sample, the average being 82 per cent.<sup>16</sup>

Finally, we<sup>17</sup> have presented evidence suggesting that pyruvic acid is a normal intermediary of carbohydrate catabolism in man. In normal persons, there is a significant rise of pyruvic acid after the ingestion of glucose, reaching a maximum at the end of one hour and returning to the normal fasting level within three hours.

The present study was undertaken to determine whether or not the peripheral neuropathy of the alcohol addict is associated with a deficiency of thiamin. Forty-eight alcoholic patients with "acute" peripheral neuropathy, 25 with "chronic" peripheral neuropathy and 22 chronic alcoholic patients without any evidence of nutritional disturbance were the subjects for this study. Pyruvic acid in the blood was determined by the method of Bueding and Wortis,<sup>15</sup> with the modifications subsequently published.<sup>18</sup> All samples were obtained on subjects fasting and at rest in bed. The method for blood determinations was also used for the spinal fluid, except that the stabilizing medium (monoiodoacetate) was found to be unnecessary. The results are shown in Figures 1 and 2.

Of the 48 cases of acute peripheral neuropathy, 45 showed an elevated blood pyruvate. In 23 of these, spinal-fluid pyruvate studies were done, and in 20 the pyruvate was abnormally high. Of the 25 cases of chronic peripheral neuropathy, all showed a normal blood pyruvate. In 10 of these, spinal-fluid pyruvate studies were done, and only 1 was elevated. The elevation in this case was very slight (1.31 mg. per 100 cc.). Of 22 cases of chronic alcoholism without any evidence of nutritional deficiency, none showed any elevation of blood pyruvate. In 14 of these, spinal-fluid pyruvate studies were normal in every case.

\*From the Medical Service of the Psychiatric Division, Bellevue Hospital, and the Department of Psychiatry and the Department of Medicine, New York University College of Medicine.

†Aided by grants from the John and Mary R. Markle Foundation, the Williams-Waterman Fund of the Research Corporation and an anonymous donor for research in psychosomatic medicine.

‡Assistant clinical professor of psychiatry, New York University College of Medicine; research fellow in psychiatry, Bellevue Hospital.

§Assistant in chemistry, New York University College of Medicine; fellow in medicine, Medical Service of the Psychiatric Division, Bellevue Hospital.

§Associate professor of medicine, New York University College of Medicine; chief of the Medical Service of the Psychiatric Division, Bellevue Hospital.

In 14 cases of acute peripheral neuropathy, pyruvic acid curves following glucose ingestion were abnormally elevated and prolonged. The maxi-

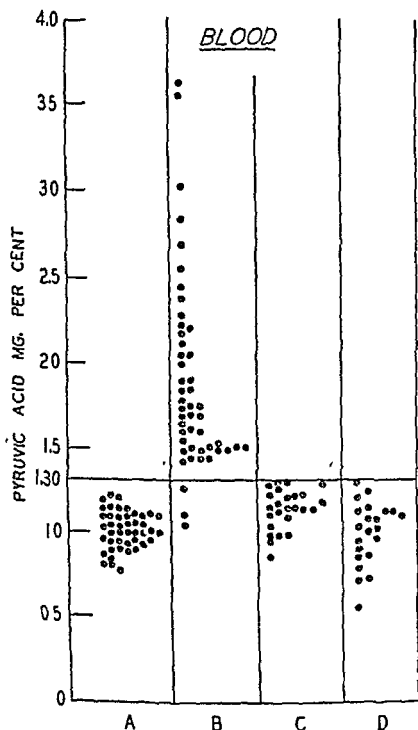


FIGURE 1 Determinations of Blood Pyruvic Acid.

A—Normal subjects, B—acute peripheral neuropathy, C—chronic peripheral neuropathy, D—chronic alcoholics without any objective evidence of nutritional deficiency

mum rise in blood pyruvate was not only greater than that seen in normal subjects, but the elevation above the fasting level was maintained for at least four hours. Furthermore, the maximum rise did not occur at the end of the first hour, as in normal persons, but the pyruvate continued to rise in every case, and maximal figures occurred at the end of the second, third or fourth hour. Particular mention must be made of one case of acute peripheral neuropathy with a normal fasting blood pyruvate, and a markedly abnormal pyruvate curve following glucose ingestion. These curves have recently been published elsewhere.<sup>18</sup>

## DISCUSSION

It will be noted that in 45 of 48 cases of acute peripheral neuropathy, the blood pyruvate was elevated. Two of the three subjects with normal fasting blood pyruvates showed no response to thiamin therapy; as a matter of fact, they grew progressively worse, despite very adequate nutritional therapy. These were the only cases in the

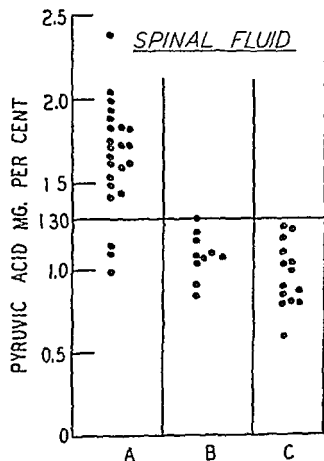


FIGURE 2 Determinations of Cerebrospinal Fluid Pyruvic Acid

A—Acute peripheral neuropathy, B—chronic peripheral neuropathy, C—chronic alcoholics without any objective evidence of nutritional deficiency.

entire group that showed no response to vitamin therapy. In the third case, the normal fasting blood pyruvate was associated with a marked abnormality in the pyruvic acid curve following glucose ingestion; the blood pyruvate was of the type that we have seen in 14 cases of acute peripheral neuropathy thus far studied. This may indicate that the pyruvic acid curve following glucose ingestion is a more sensitive index of thiamin deficiency than the fasting blood pyruvate is.

In 3 of these cases, the urinary keto acid excretion after the ingestion of glucose was studied and found to be within normal limits. During this period, the pyruvic acid curve was abnormally elevated and prolonged. This confirms Waelsch's<sup>19</sup> evidence that the origin of urinary keto acid is not related to the carbohydrate intake. It also indicates that urinary pyruvate levels cannot be used as evidence of deficient pyruvic acid metabolism in man.

We wish furthermore to call attention to the fact that these cases of acute peripheral neuropathy are invariably associated with some type of disturbance in cortical functioning.<sup>20</sup> This varies from simple disorientation with memory gaps, through delirium tremens, the Korsakoff syndrome and the Wernicke syndrome.

The Wernicke syndrome is invariably associated with a thiamin deficiency,<sup>21, 22</sup> but evidence has been presented that it is usually the result of a multiple nutritional deficiency.<sup>22</sup> The other encephalopathic syndromes may also be related to specific nutritional deficiencies, but the evidence presented to date is not conclusive.<sup>23</sup>

It is also essential to emphasize the fact that the modalities most seriously involved (touch, position and vibration) in the peripheral neuropathy of alcohol addicts are those which are eventually to be carried in the dorsal columns of the spinal cord. Alcoholic patients frequently show dorsal sclerosis at post-mortem examination. Clinically, the loss of position sense, vibration sense, light touch and plantar dysesthesia may all be duplicated by lesions in the dorsal columns of the spinal cord.<sup>24, 25</sup> It is therefore virtually impossible to tell whether or not any case of peripheral neuropathy in the alcohol addict is complicated by dorsal sclerosis.

These cases not only show involvement of the peripheral nerves, but also are invariably complicated by disorders in cerebral functioning and perhaps also in the functioning of the dorsal columns of the spinal cord. This becomes readily explicable if one realizes that the brain<sup>26</sup> and spinal cord<sup>27</sup> utilize carbohydrate as their preferential foodstuff, and that this utilization is necessarily interfered with if certain enzyme and co-enzyme systems necessary for the proper breakdown of carbohydrate are lacking.

The patients with chronic or residual peripheral neuropathy showed normal figures. These cases include those who had received adequate vitamin therapy without a complete return to normal functioning of the peripheral nerves and persons who had been on hospital diets for some time. It is possible, however, that many of the latter still show an inability to catabolize pyruvic acid properly, under the additional stress of metabolizing ingested glucose. Such studies are now under way. It has been previously suggested that in cases in which thiamin therapy had not been completely successful, irreversible pathologic changes had occurred.<sup>28</sup> These cases in which the metabolic upset had been corrected but nerve involvement persisted seem to confirm this suggestion. On the other hand, such cases may actually have a cer-

tain amount of dorsal sclerosis, and it is quite possible that thiamin therapy is of no help. Finally, many of these cases of so-called "irreversible" peripheral neuropathy frequently show marked improvement if a diet rich in other nutritive essentials is added to the thiamin therapy. Knowledge of normal nerve metabolism is by no means complete, and as additional light is shed on these other factors, it may be that certain cases of irreversible peripheral neuropathy will prove to be completely reversible.<sup>29</sup>

In the 22 cases of alcoholism without involvement of the central or peripheral nervous system, — and without any other evidence of nutritional disturbance, — the pyruvic acid levels in the blood and spinal fluid were normal. These results indicate that elevations in blood pyruvate are related to the nutritional disturbances that complicate chronic alcoholism and not to chronic alcoholism as such.

In addition, we<sup>30</sup> have studied 280 cases of various neuropsychiatric and medical disorders unassociated with any clinical evidence of thiamin deficiency, and all showed normal levels of pyruvic acid in the blood. On the other hand, we have noted hyperpyruvemia in 22 of 35 cases, complicated by marked elevations in temperature and unassociated with any clinical evidence of thiamin deficiency. In these, the elevation in total metabolism may be a result of prolonged fever, which so increases the thiamin requirements of the body that a deficiency occurs, and hyperpyruvemia results. On the other hand, it must be noted that none of these cases had peripheral neuropathy. This suggests either that the metabolic disturbance must exist for some time before peripheral neuropathy occurs or that hyperpyruvemia may be related to other metabolic disturbances in addition to thiamin deficiency. We also wish to emphasize the fact that we do not believe that a normal fasting pyruvate level invariably constitutes evidence of thiamin adequacy, and we recommend that when doubt exists, the patient be subjected to the additional stress of metabolizing ingested glucose. An inability to metabolize this substance properly is further evidence of a deficiency in thiamin.

Our results suggest that acute peripheral neuropathy in the alcohol addict is invariably associated with a deficiency in thiamin. It must be understood, however, that this does not necessarily mean that a deficiency of thiamin is the only cause of peripheral neuropathy in the alcohol addict, and we are quite certain that, in some cases, recovery is markedly expedited if other factors of the vitamin B complex are given in addition to thiamin.

As a matter of fact, Wortis, Wortis and Marsh<sup>31</sup> noted that 18 such patients showed a marked diminution in the vitamin C levels of the blood and spinal fluid. The authors did not believe that vitamin C deficiency was causally related to the peripheral neuropathy, but stated that these findings indicated the importance of nutritional factors in the nervous and mental disorders that complicate chronic alcoholism.<sup>32</sup>

Our results, however, seem to indicate very clearly that acute peripheral neuropathy in the alcohol addict is associated with hyperpyruvemia. One of the recognized causes of hyperpyruvemia is thiamin deficiency. These cases with hyperpyruvemia invariably respond to thiamin therapy with a reduction of pyruvic acid levels to normal. This correction of the metabolic defect is usually associated with clinical improvement, but rarely with clinical cure.

#### SUMMARY AND CONCLUSIONS

Patients with "acute" peripheral neuropathy almost invariably show hyperpyruvemia. This is not true of patients with "chronic" peripheral neuropathy, or of patients with chronic alcoholism unassociated with nutritional disturbances.

In 14 cases of acute peripheral neuropathy in the alcohol addict, the pyruvic acid curve following glucose ingestion was abnormally elevated and prolonged.

Disturbances in cerebral functioning, and possibly in the functioning of the spinal cord, are invariably associated with acute peripheral neuropathy.

The relation of hyperpyruvemia to cases of acute peripheral neuropathy suggests that this disease is associated with a deficiency of thiamin. On the other hand, data are presented to indicate that other nutritive essentials may well play a role in the picture as it is usually seen.

#### REFERENCES

- Jolliffe N. Vitamin deficiencies and liver cirrhosis in alcoholism: introduction polyneuropathy. *Quart J Studies on Alcohol* 1:517-557, 1940
- Swank, R. L. Asian thiamin deficiency: correlation of pathology and clinical behavior. *J Exper Med* 71:693-702, 1940
- Zimmerman, H. M., and Cowdell, G. R. Lesions of the nervous system in vitamin deficiency. IV. The effect of carotene in the treatment of the nervous disorders in rats fed a diet low in vitamin A. *J Nutrition* 11:411-423, 1936
- Zimmerman, H. M. The pathology of the nervous system in vitamin deficiencies. *Vale J Biol & Med* 12:23-28, 1939
- Ko'b L. C., Wintrobe, M. M., Kluhsatt, C., Miller, J. L., Jr., Lisco, H., and Stein, H. J. Degeneration of the primary sensory neurons in pigs from nutritional deficiency. *Tr. Am Neurol* 4: 67-189, 1941
- Bang, I., Ochoi, S. and Peters R. A. Pyruvate oxidation in brain: some diffusible components of pyruvate oxidation system. *Biochem J* 33:1940-1946, 1939
- Lu, G. D. Studies on metabolism of pyruvic acid in normal and vitamin B<sub>1</sub> deficient states: blood pyruvate levels in rat, pigeon, rabbit and man: relation of blood pyruvate to cardiac changes. *Biochem J* 33:774-786, 1939
- Platt, B. S., and Lu, G. D. Chemical and clinical findings in beri beri with special reference to vitamin B<sub>1</sub> deficiency. *Quart J Med.* 5: 355-373, 1936
- Thompson, R. H. S. and Johnson R. E. Blood pyruvate in vitamin B<sub>1</sub> deficiency. *Biochem J* 29:694-700, 1935
- Bancroft, G. G., and Harris L. J. Methods for assessing level of nutrition. Carbohydrate tolerance test for vitamin B<sub>1</sub> experiments with rats. *Biochem J* 33:1346-1355, 1939
- Wilkins, R. W., Weiss, S., and Taylor F. H. L. Effect and rate of removal of pyruvic acid administered to normal persons and to patients with and without "vitamin B deficiency". *Ann Int Med* 12:938-950, 1939
- Wortis, H., Bueding, E. and Wilson W. F. Bisulfite binding substances (B B S) in blood and cerebrospinal fluid. *Proc Soc Exper Biol & Med* 43:279-282, 1940
- Idem. Clinical significance of bisulfite binding substances (B B S) in the blood and cerebrospinal fluid. *Am J Psychiat* 97:573-588, 1940
- Robinson, W. D., Melnick, D., and Field H., Jr. Correlation between the concentration of bisulfite binding substances in the blood and the urinary thiamin excretion. *J Clin Investigation* 19:483-488, 1940
- Bueding E. and Wortis, H. Stabilization and determination of pyruvic acid in the blood. *J Biol Chem* 133:585-591, 1940
- Idem. Pyruvic acid in blood and cerebrospinal fluid. *Proc Soc Exper. Biol & Med* 44:245-248, 1940
- Bueding, E., Stein, M. H., and Wortis, H. The formation of pyruvic acid following glucose ingestion in man. *J Biol Chem* 139:793, 1941
- Idem. Pyruvic acid curves following glucose ingestion in normal and thiamin deficient subjects. *J Biol Chem* (in press)
- Waelsh, H. Excretion of keto acids. *J Biol Chem* 140:313, 1941
- Wortis, H., and Jolliffe, N. The present status of vitamins in nervous health and disease. *New York State J Med* 41:1461-1470, 1941.
- Alexander, I. Wernicke's disease. *Am J Pub H* 16:61-70, 1940
- Jolliffe, N., Wortis, H., and Fein H. D. The Wernicke syndrome. *J Nerv & Ment Dis* 93:214-220, 1941
- Jolliffe, N., and Wortis, H. Encephalopathia alcoholica. *Am J Psychiat* (in press)
- Stein, M. H., and Wortis H. Tabes dorsalis: an evaluation of the sensory findings. *Arch Neurol & Psychiat* (in press)
- Wortis, H., Stein, M. H., and Jolliffe, N. Peripheral neuropathy, an evaluation of the sensory findings. *Arch Neurol & Psychiat* (in press)
- Himwich, H. E., and Nahum, L. H. The respiratory quotient of the brain. *Am J Physiol* 101:446-453, 1932
- Wortis, S. B. The metabolism of brain, spinal cord and meningeal tissue. *Am J Psychiat* 93:87-105, 1936
- Goodhart, R., and Jolliffe, N. Effects of vitamin B (B<sub>1</sub>) therapy on polyneuritis of alcohol addicts. *J M. J.* 110:414-419, 1938
- Wortis, H., and Bueding E. Clinical significance of pyruvic acid content of blood and cerebrospinal fluid. *Tr. Am Neurol* 4: 66-90, 1941
- Bueding, E., Wortis H., Stein, M. H. and Jolliffe, N. Pathological variations in blood pyruvic acid. *J Clin Investigation* 20:441, 1941.
- Wortis, H., Wortis S. B. and Marsh, E. L. Vitamin C studies in alcoholics. *Am J Psychiat* 94:911-912, 1938
- Idem. Role of vitamin C in metabolism of nerve tissue. *Arch Neurol & Psychiat* 39:1055-1066, 1938

## REGIONAL ANESTHESIA: ITS USE IN OBSTETRICS AND GYNECOLOGY\*

EDWARD G. WATERS, M.D.†

JERSEY CITY, NEW JERSEY

A SERIOUS and circumspect view of the physiologic considerations that surround the production of anesthesia and the anesthetic needs of a patient inevitably impresses one with the indispensability of regional anesthesia.

Before the methods to be used are considered, it may not be amiss to recall that they all require definite anatomic knowledge, and that generally osteologic prominences serve to localize the approaches to the nerves and help visualize the paths they traverse. A knowledge of the peripheral distribution of the nerves supplying the operative field and the involved structures is equally essential in deciding the optimum injection points. For, obviously, the right nerves must be reached in the best location, with an adequate amount of anesthetic solution, to produce a satisfactory type of anesthesia.

### SENSORY NERVE SUPPLY

The female external genitalia receive their sensory nerve supply from the pudendal plexus, through the pudic nerves and the pudendal branches of the small sciatic nerves, which supply the larger part of the vagina, the labia minora and the posterior half of the labia majora. The anterior portions of the labia majora are innervated by the terminations of the ilioinguinal and genitocrural nerves, and infrequently by the iliohypogastric, which originate in the first two lumbar nerves. The perianal tissues and skin are also served by the coccygeal plexus.

The pudendal plexus is formed by the anterior collateral branches of sacral plexus, the fourth and fifth sacral nerves and the coccygeal nerves, in addition to sympathetic-system filaments. The pudendal plexus is really an inferior continuation of the sacral plexus. It divides into visceral and muscular branches, and in it originate the small sciatic and pudic nerves and sacrococcygeal plexus. The visceral branches unite with the hypogastric plexus and sympathetic filaments to form the pelvic plexuses supplying the bladder, the rectum, and the cavernous and uterovaginal plexuses.

The muscular branches, which supply the levator ani, coccygeus and external sphincter ani, af-

ford sensory fibers to the skin over the tip of the coccyx and base of the ischiorectal fossa.

The small sciatic nerve is entirely sensory, arising from the first, second and third sacral nerves, and leaving the pelvis through the great sacrosciatic foramen, runs to the mid thigh, posterior to the great sciatic nerve.

The inferior pudendal nerve leaves the small sciatic nerve at the lower margin of the gluteus maximus muscle, curves below the ischial tuberosity, and passing into the fold between thigh and perineum, enters the deep fascia lateral to the ischiopubic ramus. From there, its terminal branches go to the labia majora and clitoris.

The pudic nerve originates from the second, third and fourth sacral nerves, emerges from the pelvis through the greater sacrosciatic notch, rounds the ischial spine, and re-enters the pelvis through the small sacrosciatic notch. It immediately gives off the inferior hemorrhoidal nerve, and enters Alcock's canal, a fascial compartment on the medial aspect of the obturator internus muscle. It emerges at the inner and forward aspect of the ischial tuberosity and, at the base of the triangular ligament, divides into its terminal branches, the internal and external perineal nerves and the dorsal nerve of the clitoris. The pudic nerve, therefore, supplies the perianal skin and sphincter, the perineum and part of the labia majora, the perineal and external urethral muscles and the clitoris.

The sacrococcygeal plexus, formed by the fourth and fifth sacral and coccygeal nerves, supplies the pericoccygeal skin and tissues forward to the anus.

Thus, it is seen that the nerve supply of the external genitals is derived mostly from the anterior collateral branches of the sacral plexus and the pudendal plexus (lower sacrals) and the coccygeal nerves, with sympathetic-nerve contributions. The lumbar plexus contributes through the ilioinguinal, genitocrural and occasionally the iliohypogastric nerves. To effect anesthesia, one must block all these nerves.

### METHODS OF REGIONAL ANESTHESIA

The region may be anesthetized in several ways: by intraspinal block, the procedure of choice in all fat and difficult women; by sacral block; and by perineal field block.

\*Presented before the Alumni Society of the Boston Lying-in Hospital, March 14, 1941.

From the Margaret Hague Maternity Hospital, Jersey City, New Jersey.

†Assistant clinical professor of obstetrics and gynecology, Columbia University College of Physicians and Surgeons, New York City; division chief, Margaret Hague Maternity Hospital.

### *Intraspinal Block*

It is not my purpose exhaustively to discuss spinal anesthesia, but a few simple facts concerning it may be worth recalling. It differs from other types of central nerve block in that it is subdural rather than extradural. Induction requires puncture of the dura mater and subarachnoid placement of the anesthetic solution. There must be a minimum of local trauma in introducing the anesthetic. This means proper position of the patient, the use of a good flexible needle of small gauge, and avoidance of contact with the periosteum and, especially, with the intervertebral disk and nerve radicles. Adherence to these rules resolves itself into experience and the knowledge of anatomy. Bad results are generally due to lack of fundamental knowledge and inept technic.

Once placed, the anesthetic and its effects are largely beyond control. Hence, the amount and placement level must be conditioned by the patient and the operation to be done. For abdominal, gynecologic and obstetric operations, the level is the third space, with 100 to 120 mg. novocain diluted in spinal fluid to a volume of 3 or 4 cc. In a prolonged case, 8 to 10 mg. of Pontocaine is added. For vaginal work and deliveries, 50 mg. of novocain is similarly diluted and placed intrathecally in the fourth space. The patient is kept flat on the table, or a moderate Trendelenburg position may be used if the patient is not pregnant or if there is no large abdominal tumor, intraperitoneal fluid or marked distention. Ephedrine sulfate,  $\frac{3}{4}$  gr. hypodermically before induction of anesthesia, lessens blood-pressure fall, although this in itself is unimportant provided the pulse remains good and the respirations are not embarrassed. If respiratory embarrassment occurs, immediate inhalation use of oxygen under pressure and intravenous fluids are invariably effective. I have given over three thousand spinal anesthetics, with but one death that could be ascribed to the anesthetic; I admit, however, a few close calls. In the Margaret Hague Maternity Hospital, we have administered over five thousand spinal anesthetics in the past eight years, with three deaths that could be ascribed, with any reason, to the type of anesthetic given. It scarcely needs saying that we should have long since given it up had we found the dangers even remotely as present as its antagonists contend. The vast majority of the detractors of the procedure have had little or no experience with it and possess an inferior technic. We do not claim it to be the 'only anesthetic to use or the best in every case, and it has definite contraindications. But it is a very good and very safe anesthetic when properly employed, and its use

is not infrequently the major factor in a patient's recovery from a difficult plight.

### *Sacral Block*

Unfortunately, the facility of administering a spinal anesthetic has obscured the value of another form of nerve block — trans-sacral, with caudal, block. This is a perfectly safe type of anesthesia that is only moderately difficult to employ. The combination has the virtues of subdural block, with none of the hazards. The objections are the time it takes, frustrating fat and, in pregnancy, inability to obtain the optimum induction position.

Although I admit that sacral block has taken a poor third place to spinal anesthesia and local infiltration in pelvic, perineal and rectal work in my own hands, it is a good type to have in reserve for special conditions. For cases of hypertensive cardiac disease or pre-eclamptic toxemia with respiratory infection, or in any other case in which a spinal anesthesia might be somewhat hazardous or the patient is suffering with an upper respiratory infection of any degree, a sacral block is ideal.

The technic may be rather simply and quickly set down, thanks to the pioneering work of Labat<sup>1,2</sup> and others,<sup>3-7</sup> who have so well standardized its application. If the prone position, with a cushion under the patient's hips to raise the sacrum, is not possible, the next best one is the extreme Sims. Caudal block is first induced, since it takes about twenty minutes for it to be effectively obtained and because it fails in 10 to 20 per cent of cases. For caudal block, the puncture is made in the sacral hiatus in the middle of a triangle formed by the sacral cornua and the fourth sacral spine. The sacral hiatus is palpated with the finger, after which the needle is introduced with the bevel upward at an angle of 20° with the skin. The needle passes through the ligament and forward to the anterior wall of the canal; it is then retracted and depressed 20° farther. It is then introduced as far forward as a line joining the posterosuperior iliac spines. This marks the average lower depth of the dural-sac level. It is essential not to carry the puncture farther, and not to introduce the solution if spinal fluid is then obtained. Thirty cubic centimeters of a 2 per cent novocain solution is injected or if parasacral block is also employed, it is better to use 30 cc. of a 1 per cent novocain solution. I generally add about 5 minims of epinephrine solution, about 0.5 mg. to each 100 cc. of anesthetic employed.

Paravertebral sacral block may then be proceeded with. The landmarks here are the sacral cornua and the posterosuperior iliac spine. As a matter of fact, the point most commonly chosen for the



latter is the regional posterior spine, which is the last prominence at the posterior extremity of the iliac crest, usually about 1 cm. above the anatomic spine. The sites of injection are chosen as follows: wheals are raised 1 cm. medial to and below the regional posterior spine, with another wheal lateral to and just above the sacral cornua; a line, which is drawn between these two points and beyond the posterosuperior spine, is divided between the two chosen points into three equal parts, with two wheals of novocain. The ilial or uppermost wheal marks the aperture of the second sacral foramen. The cornual wheal marks the site of the fifth sacral foramen. The other two wheals, marked out between these, locate the third and fourth sacral foramina. The first sacral foramen is punctured through a wheal raised 3 cm. on the line above the ilial or first wheal. The manner of injection is as follows: The bone is met on the dorsum of the sacrum before the foramen is perforated, and the needle is then passed in for varying distances. It is probably easiest to remember that from the first to the fifth foramina, respectively, the distances that the needle enters after touching the bone diminishes by 0.5 cm.—from 2.5 to 0.5 cm.—for each foramen, and the amount of novocain, a 1 per cent solution being used, diminishes from 6 to 2 cc., being reduced 1 cc. for each foramen. This, then, permits the introduction of 20 cc. of novocain solution on each side of the sacrum in contact with the sacral nerves as they emerge from the anterior surface of the sacrum; the radicles of the sacral and perineal plexuses are thus blocked. Anesthesia here follows very promptly, and by the time of its completion, caudal anesthesia is generally effective if it is to become so.

### *Perineal Field Block*

There are several effective ways of obtaining a satisfactory perineal field block; the one that I routinely employ, which has proved satisfactory, is not claimed to be better than any one of the other methods used, but it has repeatedly given and continues to give satisfactory results.

The principle employed is the blocking of nerves supplying the vulval and perineal region as they approach that area. The main injection involves blocking the pudic nerve as it emerges from Alcock's canal near the ischial tuberosity. The other nerves are blocked as their terminations approach the field. The first injection is made through a wheal raised over the ischial tuberosity. A 10-cm. needle is introduced, and bony contact is first made with the ischial tuberosity; it is then passed 2 cm. medial to and 2 cm. deeper than the tuberosity. This is approximately the point at

which the pudic nerve emerges from Alcock's canal. Fifteen cubic centimeters of a 1 per cent solution of novocain, with ephedrine, is injected at this site on both sides. The needle is then withdrawn, reintroduced and conducted subcutaneously about 0.5 to 1 cm. deep across the perineum to the ischial wheal on the opposite side. It is then withdrawn and directed from both wheals backward toward the anus until injections are made into the sphincter muscle itself. Reintroduced through the ischial wheals, the needle is directed obliquely inward toward the introitus, then deflected sharply upward along the inner aspect of the vestibular bulb and under the labia minora, distending the structures with novocain as far forward as the clitoris. Thus, a diamond-shaped block of the introitus is evolved. The transverse bischial infiltration with the anterior limbs blocks the ilioinguinal, iliohypogastric and genitocrural nerves, the pudendal branch of the small sciatic nerve and, partly, the internal and external branches of the pudic. The posterior arms block the hemorrhoidal branches of the pudic nerve and the terminations of the anococcygeal plexus, and paralyze the anal sphincter. Direct infiltration of the pyramidal perineal body permits immediate, deep, perineotomy.

When the innervation of the external genitals is recalled, it is apparent that not only the sensory but also the muscular nerves of these structures are effectively blocked, and anesthesia is produced for a third or half of the way up the vagina. One must also remember that, even with an outlet-forceps application, the blade tips are far in the vagina, where there is less sensation but also no anesthesia, and anesthesia should therefore be supplemented with deliberate and gentle movements. For deep vaginal work in gynecology, submucosal local infiltration is added, as well as a broad ligament block for cervical procedures, to anesthetize the uterine and vaginal sympathetic plexuses. It is recommended that adrenalin always be added to the anesthetic solution. In obstetrics, the extreme vascularity of the parts causes a rapid washing out of novocain, with anesthetic failure, unless this precaution is taken.

39 Gifford Avenue

### REFERENCES

1. Labat, G. Personal communication.
2. *Idem*. Paravertebral sacral block. In *Regional Anesthesia: Its technique and clinical application*. 496 pp. Philadelphia: W. B. Saunders Co., 1922. Pp. 251-269. Caudal block. Pp. 272-286.
3. Baptisti, A., Jr. Caudal anesthesia in obstetrics. *Am. J. Obst. & Gynec.* 38:642-650, 1939.
4. Gellhorn, G. Local anesthesia in gynecology and obstetrics. *Surg., Gynec. & Obst.* 45:105-109, 1927.
5. Bradford, W. Z. Selection of obstetrical anesthesia with special reference to local infiltration. *South. Med. & Surg.* 98:19-22, 1936.
6. O'Hearn, E., and Knauer, C. H. The technique of injection of the pudendal nerve and branches of the small sciatic nerve with observations made on one hundred cases of delivery. *Am. J. Obst. & Gynec.* 26:444-446, 1933.
7. Greenhill, J. P. Local, infiltration anesthesia in obstetrics. *Southern M. J.* 26:37-44, 1933.

## MEDICAL PROGRESS

### HEMATOLOGY: DISEASES OTHER THAN ANEMIA

WILLIAM DAMESHEK, M.D.\*

BOSTON

#### BONE MARROW

THE sternal bone-marrow biopsy, performed chiefly by means of the simple puncture technic, has become almost a routine hematologic procedure. Not only is it of value in the differential diagnosis of so-called "refractory anemia," "princytopenia" and so forth, but it is distinctly a necessary maneuver in ruling out leukemia in cases of both thrombopenic purpura and hemolytic anemia, especially when splenectomy is being seriously considered. The physician who familiarizes himself with the technic will gradually develop a better understanding of the physiologic pathology underlying the various blood pictures. Since the latter may give only an imperfect reflection of what goes on in the blood forming tissues, careful study of the marrow should be of real help in developing a fundamental knowledge of the blood conditions. To learn "to walk about" in the marrow requires only a little instruction but a good deal of practice and patience. In any event, interpretation of bone marrow pictures is not nearly so difficult as it seems at first glance.

Probably the best monograph thus far on the bone marrow (in German) is that by Rohr,<sup>1</sup> of Zurich, Switzerland.

Recently, the sternal bone marrow has been utilized for therapeutic purposes. Thus, Morrison and Samwick<sup>2</sup> cite the case of a patient with aplastic anemia who was given several injections of normal sternal marrow, totaling 13 cc, obtained from compatible donors. The patient recovered. It is to be noted that just prior to the bone-marrow "transfusion," the patient's blood showed well-defined evidences of increased regenerative activity on the part of the marrow, that is, marked polychromatophilia and the presence of nucleated red cells. Frequent reticulocyte and platelet counts were not performed. Various other forms of therapy, such as liver extract and iron, were also used. It is highly doubtful whether the few cubic centimeters of actual normal bone-marrow tissue

injected into the sternum had any effect on an organ that approximates about 1400 cc. in volume.

Fluids and blood injected into the sternal marrow cavity quickly reach the venous circulation, as demonstrated by Tocantins and O'Neill.<sup>3</sup> These investigators, after a thorough study of the sternal marrow in various age groups, devised a special needle and adapter by which, in an emergency, it is possible to transfuse into the sternal cavity large quantities of blood or saline solution. This might conceivably be important in a case with extensive burns or when the veins are collapsed or inaccessible.

#### FRAGILITY TESTS

The methods in general use for determining hypotonic fragility are quite inaccurate. The method most commonly employed, that of Giffin and Sanford, utilizes unmeasured drops of blood, which are placed in tubes containing only roughly estimated amounts of hypotonic saline solution. In the procedure of Daland and Worthley,<sup>4</sup> the solutions and the amount of blood are accurately measured. Furthermore, the blood is adjusted to constant volume so that even in the presence of severe anemia, approximately the same number of red cells are added to similar volumes of saline solution. Even this method, however, leaves room for improvement, since the tube in which beginning hemolysis is present is often difficult to define and the other readings are also more or less subjective. To avoid these disadvantages, Waugh and Asherman<sup>5</sup> used the Evelyn photoelectric colorimeter and measured the degree of hemolysis directly. By this method, curves of erythrocyte fragility measuring the percentage of hemolysis with the various solutions of hypotonic saline could be drawn. In a later paper, Waugh and Lamontagne<sup>6</sup> illustrated an application of this method in the study of the changes in fragility following splenectomy in congenital hemolytic jaundice. Hunter<sup>7</sup> has recently described a similar method, and Cruz and his co-workers<sup>8</sup> also utilized this method in a unique study with radioactive iron of the effect of age on the susceptibility of the erythrocyte to hypotonic saline solutions. The latter authors injected radioactive iron into dogs rendered anemic by

\*Reprints of articles in this series are not available for distribution but the articles will be published in book form. The current volume is *Medical Progress Annual 1940* (Springfield, Illinois: Charles C. Thomas Company, 1941) \$4.00.

\*Assistant professor of medicine, Tufts College Medical School, visiting physician and consulting hematologist, Joseph H. Pratt Diagnostic Hospital, 41 of Blood Clinic, Boston Dispensary.

bleeding. This "tagged" iron is present only in the young red cells, — reticulocytes, — and it was thus thought that an accurate determination of the relative fragility of older as against younger red cells could be made. The surprising result was obtained that the very new red cells in the circulation were "markedly less resistant" to hypotonic saline solutions than the older cells. Unfortunately, this type of experiment probably does not yet completely solve the vexing question whether younger or older red cells are more fragile.

#### BLOOD VOLUME

Gibson has been in great part responsible for perfection of the blood-volume test that utilizes the Evelyn photoelectric colorimeter and the Evans blue dye. In a recent article,<sup>9</sup> a general review of his findings is presented. In the diagnosis and follow-up of a case of polycythemia, determination of the blood volume is often of great value. In studies of hemolytic anemia, the relation of the total mass of hemoglobin to the urobilinogen content of the feces gives an index of blood destruction that is at times of diagnostic value.<sup>10</sup> Although the Gibson-Evelyn method for determining the blood volume is universally conceded to be the most accurate, Ebert and Stead<sup>11</sup> have recently criticized it because the cell-volume reading depends on the hematocrit and this factor is difficult to determine accurately. The latter investigators showed that the relative proportion of red cells varied considerably in different blood vessels of the body, and that the basing of the hematocrit on determinations made from basilic veins might lead to error. This has, of course, been well known, but is difficult to get around, unless some such method as that of Barcroft (utilizing carbon monoxide) is used.

Hahn, Ross and their co-workers<sup>12</sup> have devised another interesting method, which has not yet been applied to human beings. From a dog injected with radioactive (tagged) iron, a known amount of blood is injected in other dogs, and the blood volume calculated from the relative amount of radioactivity present in the injected dog's blood.

#### TESTS OF BLEEDING TIME

The test in use for many years is that of Duke, in which a puncture of the ear is made, the resulting wound being blotted every thirty seconds. Ivy, Shapiro and Melnick<sup>13</sup> attempted to make the test more accurate by pricking the skin of the forearm under conditions of venostasis — a blood-pressure cuff being inflated over the arm to a pres-

sure equivalent to 40 mm. of hemoglobin. In a more recent article, Ivy, Nelson and Bucher<sup>14</sup> report on the standardization of the various factors of pressure, type of puncture, type of blade used and so forth. By this method, the bleeding time varies between sixty-one and two hundred and forty seconds.

#### BLOOD GROUPS

##### *Rh Factor*

One of the outstanding examples of progress in hematology during 1941 has been the development of knowledge concerning the Rh factor. Landsteiner and Wiener<sup>15</sup> showed in 1940 that by the injection of blood cells of the monkey — *Macaca rhesus* — into rabbits, an antirhesus red-cell agglutinin was built up in the rabbit serum. Curiously enough, it was found that this agglutinin (called "anti-Rh") also agglutinated the red cells of most human subjects, without reference to the regular human blood groups (O, A, B or AB). Further studies by Wiener and Peters<sup>16</sup> demonstrated that the cause of certain severe blood-transfusion accidents, involving donors and recipients of the same blood group, lay in the presence of this anti-Rh agglutinin in the recipient, reacting against the donor's susceptible red cells, which contained an Rh binding substance or agglutino-gen; such persons are said to be "Rh+." Levine and his co-workers<sup>17</sup> demonstrated that approximately 85 per cent of 1035 persons were Rh+, and 15 per cent Rh-. Thus, if an Rh- subject (that is, one having no Rh agglutino-gen in his red cells) is given blood from a donor with Rh+ cells, a reaction will occur if the recipient's serum contains the anti-Rh agglutinin. Only an Rh- person can possess anti-Rh agglutinin in the serum, since the two substances are mutually incompatible. It was further found that most of the transfusion reactions involving the Rh factor occurred in women, either pregnant or in the puerperium, who had been given blood from their husbands. Analysis of several of these cases by Wiener and Peters<sup>16</sup> and Levine and his co-workers<sup>17</sup> demonstrated that the recipient was Rh- but had an anti-Rh factor in her serum, and that the husband donor was an Rh+. The possibility was suggested that the mother might have become immunized against her husband's red cells by way of the fetus (which usually was Rh+). The concept of isoimmunization in the human being by the Rh factor was thus developed.

Shortly thereafter, Levine, Katzin and Burnham<sup>18</sup> pointed out that in cases of erythroblastosis foetalis, the following combination of facts was present: the mother was Rh- and often showed

\*Dr. J. F. Ross of the Evans Memorial, Massachusetts Memorial Hospitals, has recently applied this method to human blood-volume determinations by injecting tagged red cells from previously injected polycythemic patients into other persons.

anti Rh agglutinin in her serum, the father was Rh+, and the infant was Rh+. It was suggested by these workers, and borne out by analysis of repeated cases, that some Rh- mothers might become immunized to the Rh factor if the baby's red blood cells passed into the general circulation via the placenta. When this had taken place, an agglutination reaction might occur within the placental tissues, damaging the red cells and producing the clinical picture of erythroblastosis foetalis in the newborn infant. This rather startling although attractive theory of isoimmunization as an explanation of the pathogenesis of the disorder has already aroused a great deal of interest and may be of considerable practical significance.

To test a subject for the presence or absence of Rh factor in the red cells, it is necessary to have anti Rh testing serums. These are not now readily prepared, and reliance must be placed on human subjects who have developed an anti Rh substance in the serum. Since these are relatively scarce and since, furthermore, the actual testing is somewhat more delicate and "tricky" than ordinary blood typing, it becomes essential for the practicing physician to observe the following rules regarding transfusions of blood. In the first place, compatibility tests, particularly with patients who are pregnant or in the puerperium, or who have had previous transfusions, should be performed by the Landsteiner test tube technique. One drop of the serum to be tested, one drop of a 2 per cent red cell suspension and one drop of physiologic saline solution are placed in small test tubes, incubated at 37°C for thirty to sixty minutes, and centrifuged for one minute at slow (500 RPM) speed, and the sediment of the tube is inspected<sup>19</sup> and the tube observed for clumps—a definitely positive reaction is readily observed with the naked eye, and a negative reaction should be checked by microscopic examination of the sediment. Secondly, if a transfusion is required in pregnancy or the puerperium, it is best not to use the husband as a donor. And, finally, in erythroblastosis foetalis, one should go to great lengths in obtaining an Rh- donor for the infant, and in performing exceedingly careful cross-matching tests preliminary to transfusions; the infant's mother should not be used as a donor. The further general suggestions might be made before a transfusion is given, the question whether it is really necessary should be asked, and typing and cross-matching should not be performed by the most inexperienced junior on the service. Correct typing and cross matching before a transfusion are important tests and deserve the utmost care; they are best done by competent unhurried workers.

### Miscellaneous Data

Group A (Type II, Moss) is known to be made up of Subgroups A<sub>1</sub> and A<sub>2</sub>. With the use of high-potency testing serums,\* cells of Group A or Group AB can almost always be distinguished. However, occasional persons of Group A or AB react feebly even to the most potent testing serums and may therefore be miscalled Group O or B. Recently, Wiener and Silverman<sup>20</sup> demonstrated that a third A agglutinin (A<sub>3</sub>) was occasionally present, and might be confusing in determining the blood group. This brings up another possible cause for transfusion reactions, which can be avoided only by very careful compatibility tests.

The preparation of anti M, anti N, anti-A and anti-B testing serums is discussed by Silverman.<sup>21</sup> The difficulties involved in preparing a potent anti-N serum are pointed out. The use of M and N testing serums in the exclusion of paternity is increasing as knowledge of the importance of these factors gradually becomes disseminated. With development of potent A<sub>1</sub>, A<sub>2</sub>, Rh and possibly other factors, it will be possible to increase the percentage of exclusions from the present approximately 40 per cent to a higher figure.

The use of the so-called "universal donor" (Group O or Type IV) may be distinctly dangerous if the recipient belongs to another blood group, because such a donor has in his serum the anti A ( $\alpha$ ) and anti B ( $\beta$ ) agglutinins. Witelsky, Klendshoj and Swanson<sup>22</sup> set about the task of isolating the A and B specific substances and then adding them to blood containing anti-A and anti-B agglutinins, thus neutralizing the possible ill effects of transfusing Group O blood. Both the A and B substances are carbohydrate-like and similar to the complex carbohydrates that are recognized as the bearers of the type specificity of pneumococci and other organisms. Addition of small amounts of these substances to blood for transfusions effectively removed the anti-A and anti-B agglutinins and did not cause reactions. These substances are not at present commercially available. They have been found of value not only in making Group O blood entirely compatible but also in neutralizing the A and B agglutinins of M, N and Rh testing serums.

The moral of this section on the blood groups might be stated as follows: transfuse only when absolutely necessary and only after extremely careful compatibility tests have been performed by responsible, experienced persons.

\*These may be obtained from the Blood Betterment Association, New York City and from Lederle Laboratories Incorporated, Pearl River, New York.

## WHITE BLOOD CELLS

*Basophils*

Doan and Reinhart<sup>23</sup> present a carefully documented discussion of the basophil (basophil granulocyte). They state that "of all the cells found in normal blood least, perhaps, is known at the present time about the basophil type of granulocyte." They cite cases indicating a possible "primary progressive specific hyperplasia of basophil granule leukocytes."

*Infectious Mononucleosis*

This very common, and rarely diagnosed, condition continues to be the subject of numerous reports. In a paper by Werlin, Dolgopel and Stern,<sup>24</sup> the possible confusion of the condition with diphtheria is discussed. In 14 of 21 cases admitted to the Willard Parker Hospital in New York City, the clinical picture was considered sufficiently suspicious of diphtheria to warrant the administration of diphtheria antitoxin on admission. The authors state:

. . . . The diagnostic difficulty was further complicated in 7 of these cases by the presence of non-toxic diphtheria-like bacilli in the throats of 6 patients and in the nose of 1 patient. The negative toxicity tests of the isolated bacilli, the hematologic picture, the positive heterophil antibody test and the lack of response to the diphtheria antitoxin helped in establishing the correct diagnosis.

Cerebral complications are quite frequent, and as Thelander and Shaw<sup>25</sup> point out, severe headache is often an early and prominent symptom. I have recently seen a number of cases in which the diagnosis of "aseptic lymphocytic meningitis" or "choriomeningitis" was made. To be sure, the spinal fluid revealed a lymphocytosis, but there was a marked lymphocytosis in the peripheral blood and the sheep-cell agglutination test was positive. Sadusk<sup>26</sup> directs attention to the temporarily positive serologic tests for syphilis, which occur in approximately 15 per cent of reported cases (only in some series, it should be noted) and indicate that a positive Wassermann or Kahn reaction is likelier to occur in the presence of a rash.

Smith<sup>27</sup> directs attention to what he calls "infectious lymphocytosis." In young patients, a transient lymphocytosis without other symptoms or signs, or a more prolonged lymphocytosis following infections of the upper respiratory tract, is not uncommon. Smith contends that these cases are frequently confused with infectious mononucleosis, but that they should be differentiated from them by the essentially normal, mature character of the lymphocytes, and by the negative heterophil reaction. This differentiation is significant, since otherwise an underlying respiratory or other infec-

tious process might be missed. Essentially, Smith's infectious lymphocytosis is simply the lymphocytic reaction commonly seen in any chronic smoldering infectious process, and does not indicate a hitherto undescribed condition. What is more, infectious mononucleosis might best be called "infectious lymphocytosis," since the cellular reaction is primarily lymphocytic and not monocytic. Acute cases of so-called "glandular fever" that resemble mononucleosis in every respect but have negative heterophil reactions are occasionally seen. Are these due to a different etiologic agent than that causing infectious mononucleosis, or are they simply heterophil negative? Since the etiologic agent has not yet been discovered, this question is difficult to answer.

*Leukocytic Reactions, including Leukopenia*

The sulfonamide drugs continue to prove a fertile source for the development of various reactions involving both the red cells and the leukocytes, although with the use of the newer drugs, sulfathiazole and sulfadiazine, the reactions seem to be distinctly lessened. Rinkoff and Spring<sup>28</sup> report 8 cases of either severe leukopenia or agranulocytosis following the use of sulfanilamide or sulfapyridine, but of 51 treated with sulfathiazole, none developed a toxic reaction. However, Kennedy and Finland<sup>29</sup> report a case of fatal agranulocytosis following the use of sulfathiazole. Plum and Thomsen<sup>30</sup> compared the agranulocytosis caused by amidopyrine with that induced by the sulfonamides and concluded that an accompanying anemia was much commoner with the latter drugs and was often associated with a rash, although severe throat lesions were less frequent. The mortality rate was distinctly less in the sulfonamide-treated cases (67 per cent). Occasionally, marked leukocytosis and even a leukemoid reaction may occur with the sulfonamides. These are usually either in association with or preceding a definite hemolytic reaction. Whether or not some of the cases of acute leukemia seen following the use of sulfonamides have any relation to the drug or are coincidental cannot be stated for certain, although since the drugs are given for almost every fever, coincidence is more than likely.

Lawrence<sup>31</sup> describes the various abnormal physiologic conditions that may result in leukopenia, grouping them as follows: those due to diminished manufacture of white blood cells (including aplasia and maturation arrest); those due to increased elimination of white blood cells; those due to an increased rate of destruction in the peripheral blood; those due to redistribution of

the leukocytes in the vascular channels; and those due to redistribution of the leukocytes in the body as a whole, as in the leukopenic phases of certain cases of leukemia. He makes a plea for a more physiologic understanding of the various causes of leukopenia. An interesting type of severe leukopenia said to be caused by an increased destruction of leukocytes by the spleen is described by Muether and his associates.<sup>32</sup> This condition, first described in a systematic way by Doan,<sup>33</sup> may be acute or chronic, and may even simulate agranulocytosis. It is often accompanied by splenomegaly, and at times by slight hemolytic jaundice. The bone marrow is hyperplastic. Splenectomy has resulted in dramatic cures. The interpretation of both the Columbus and the St. Louis workers is that the spleen destroys the leukocytes by phagocytosis. It is my belief<sup>34</sup> that splenic enlargement often causes an increase in the normal inhibitory effect of that organ in the marrow, with the result that the marrow becomes crowded with leukocytes, which are apparently prevented from being delivered to the circulating blood. Splenectomy may result in a resumption of the normal delivery mechanism. In any event, splenic leukopenia and granulocytopenia, often of striking degree, may be secondary to splenomegaly and relieved dramatically by splenectomy.

#### *Reactions to Benzol and Related Chemicals*

An increasing interest is being shown in the reactions of benzene chemicals on the blood-forming organs. Schwarz and Teleky<sup>35</sup> state that the blood picture in chronic industrial benzene poisoning is the result of a balance between destructive and regenerative forces. Instead of the classic anemia, leukopenia and thrombopenia, temporary erythrocytosis, erythroblastosis, leukocytosis with immature white cells and even leukemia may develop. Any change from the normal should be an immediate indication for the removal of the worker from the source of exposure. It is recommended that blood examinations be made monthly in workers using benzene, and every four to six months in those using related chemicals. Goldwater,<sup>36</sup> in a study of 332 workers exposed to benzol fumes in rotogravure industry in New York City, observed that anemia, macrocytosis and thrombocytopenia were the commonest abnormalities, whereas leukopenia and neutropenia were rather unusual. Not infrequently, relatively high hemoglobin values associated with elevations in the mean corpuscular volume were present. In another paper, Goldwater and Tewksbury<sup>37</sup> made a follow-up study of rotogravure workers who had developed blood changes as the result of exposure to benzol and who had then been safe-

guarded from the hazard. Toxic effects were present in some cases for at least two years. Recovery was manifested by an increase in red-cell count, a decrease in red-cell size and an increase in the platelet count. The usual forms of anti-anemic treatment appeared to have no effect in hastening recovery. Hamilton-Paterson<sup>38</sup> studied workers exposed to benzol in the rubber industry. In this series of cases, leukopenia was the commonest finding, but leukocytosis and even leukemia occasionally developed.

All these reports confirm an earlier one by Hunter<sup>39</sup> in which similar findings were made. The possibility that prolonged exposure to low concentrations of benzene might produce leukemia was first broached in this paper, and should be seriously considered. Careful histologic studies of the bone marrow and other blood-forming organs were made by Mallory, Gall and Brickley,<sup>40</sup> who showed the very variable changes—aplastic, hypoplastic, proliferative and even leukemic—that might develop. These changes depended on the intensity and duration of exposure, hyperplasia following prolonged exposure and hypoplasia of either short or long contact. The authors pointed out that although the evidence indicating that chronic exposure produces leukemia was still incomplete, it is nevertheless accumulating and worthy of serious consideration. Rawson, Parker and Jackson<sup>41</sup> state that all their 6 cases that were diagnosed as "agnogenic myeloid metaplasia" and were available for study gave a history of exposure to industrial solvents, "high-test" gasoline, carbon tetrachloride, paint remover or benzol.

#### *POLYCYTHEMIA VERA*

Primary, idiopathic or true polycythemia is a disease of the bone marrow in which striking hyperplasia of all the elements—erythroblastic, leukocytic and megakaryocytic—continues for many years. This results in great increases in the red cells, leukocytes and platelets of the blood and, finally, in a great overdistention of the entire circulation. The cause of the continued hyperplasia remains obscure, although the most attractive theory is that of anoxia of the marrow, with resultant stimulation to erythropoiesis. It should be noted, however, that anoxia (such as that at high altitudes) causes only erythrocytosis, the platelets and granulocytes remaining normal in number. Davis<sup>42</sup> showed that the oral and subcutaneous administration of both ephedrine and amphetamine (Benzedrine) caused polycythemia (erythrocytosis) in dogs and rabbits, perhaps through vasoconstriction of the vessels of the bone marrow, with resultant anoxia and stimulation of erythropoiesis. This effect occurred in both

normal and splenectomized animals and appeared to be due to a real influence on red-cell production.

The extreme viscosity of the blood, in addition to the great overdilatation of the entire circulation, leads to the development of a sluggishly moving mass of blood. Offhand, it seems that the work of the heart should be increased. However, measurements of the cardiac and respiratory function in 3 relatively young patients by Altschule, Volk and Henstell<sup>13</sup> revealed normal values, and the conclusion was made that the slowing of the blood flow was due to increased capillary resistance because of the greatly increased viscosity, which, with the slow blood flow, the greatly increased platelet count and the early onset of arteriosclerosis, is of course conducive to the development of thrombosis.

Another complication that has recently received increasing attention is that of sclerosis of the marrow usually associated with a bone-marrow type of cellular proliferation (myeloid metaplasia) in the spleen. In last year's progress report,<sup>44</sup> reference was made to a number of articles in which this end-result condition was discussed. That there is an "agnogenic myeloid metaplasia"<sup>45</sup> of the spleen, without reference to polycythemia, hemolytic anemia or involvement of the bone marrow by neoplasm, leukemia, Gaucher's disease and so forth, is questionable; nor does it seem desirable to make of this condition a separate entity. Furthermore, that bone-marrow proliferation develops in the spleen in response to bone-marrow destruction elsewhere or to unusual bone-marrow stimulation, as in severe hemolytic anemia, has been known for many years; its rediscovery under a new guise is interesting but perhaps confusing. It is also likely that many of the cases of chronic myelogenous leukemia reported following polycythemia are in reality examples of this "burnt-out" state of polycythemia, the leukocytic proliferation being unusually prominent.

In the treatment of polycythemia, all the symptoms may be quickly relieved by reducing the blood volume to normal and keeping it so. This is done by semiweekly venesections of blood for three to five weeks (depending on the case), and by the use of a diet low in iron.<sup>46</sup> On the face of it, this appears to be a more physiologic method of treatment than the use of hemolytic drugs (phenylhydrazine), a toxic drug such as lead, as suggested by Falconer,<sup>47</sup> or radioactive phosphorus.<sup>48</sup> Patients with polycythemia are relatively healthy and live for many years. The use of harmful or potentially harmful drugs seems therefore undesirable.

## HEMORRHAGIC DISEASES

The clotting of blood in blood vessels is a function of the enzyme-chemical factors, thromboplastin-prothrombin-fibrinogen, of the platelets and of the blood-vessel wall. Failure of clotting occurs in the presence of a defect in any of these three mechanisms. An analysis of 355 autopsy cases that showed one or another of these disturbances is reported by Perlman and Fox.<sup>49</sup> The suggestion is made that the term "hemorrhagic diathesis" be used, qualified by the phrase "on the basis of" damage to or weakness of the capillary endothelium, deficiency of the clot-forming elements or faulty clot retraction due to thrombocytopenia.

### *Deficiency of the Clot-Promoting Elements*

Quick<sup>50</sup> gives an excellent and detailed review of the hemorrhagic disorders due to defects in the coagulation mechanism of the blood. These may be associated with diminished prothrombin, calcium deficiency, thromboplastin deficiency, fibrinogen deficiency and, finally, the presence of anticoagulants. Ferguson<sup>51</sup> also gives a summary of his and other work on the blood-clotting anomalies in the hemorrhagic diseases. Both authors rule out calcium as having any importance in these conditions. The original reviews should be consulted for specific information on these subjects.

*Hypoprothrombinemia.* The earlier work on vitamin K deficiency and its bearing on hypoprothrombinemia has been cited in previous reviews. Recent articles have extended the groundwork already laid. The value of protecting the newborn infant from the effects of a low prothrombin level by giving the expectant mother vitamin K from five to twenty-eight days prior to delivery is pointed out by Valentine, Reinhold and Schneider.<sup>52</sup> About three quarters of the infants of untreated mothers developed a low prothrombin level within forty-eight to ninety-six hours after birth, whereas infants of protected mothers showed no such fall. It is further to be noted that one of the causes of cerebral hemorrhage of the newborn may be hypoprothrombinemia, and that the prothrombin level of the infant may be made normal by the simple injection of one of the parenteral preparations six or eight hours before delivery. That liver damage results in a diminution in the prothrombin is by now well known. Lucia and Aggeler<sup>53</sup> tried to correlate the various liver-function tests with the diminished blood prothrombin in a series of cases. No definite correlation could be determined, although some differentiation between hepatic jaundice and obstructive jaundice could be worked out by the administration of vitamin K. In the presence of hepatic disease, the prothrom-

bin clotting time could not be materially altered. Similar findings and the development of a liver-function test based on this procedure are made by Lord and Anders<sup>54</sup> A hemorrhagic agent resulting in an increased prothrombin time has been studied by Bingham, Meyer and Pohle.<sup>55</sup> This material, which was isolated and crystallized at the University of Wisconsin Agricultural Experiment Station, has been shown to be a dicoumarol. Synthetically prepared, it produced prolongation of the prothrombin and coagulation times, when given to dogs and human subjects. It is suggested that the material may prove to have a valuable place in clinical medicine as an anticoagulant to replace heparin

**Hemophilia.** Despite vigorous investigation, no very striking advance has occurred in either the pathogenesis or the treatment of hemophilia. The researches of Taylor and his collaborators at the Thorndike Memorial Laboratory, Boston City Hospital, cited in previous reviews, indicated that something was lacking in the globulin fraction of the plasma. In the meantime, the old theory that hemophilia is due to a diminution in thromboplastin formation from unusually resistant platelets has been espoused again, chiefly by Quick,<sup>56</sup> Ferguson<sup>51</sup> and Howell.<sup>57</sup> Quick described a new diagnostic test for hemophilia based on the diminished production of thromboplastin from abnormally resistant platelets. He found that the coagulation time of ovalated hemophilic plasma subjected to high centrifugation is markedly longer than that of slowly centrifuged plasma. With high centrifugation, the intact platelets are thrown down, leaving a plasma poor in both free and potentially free thromboplastin. Ferguson suggests that hemophilia is a deficiency in the plasma content of a new thromboplastic enzyme, the function of which is to mobilize calcium and cephalin for the conversion of prothrombin to thrombin. Howell considers one real difference between normal and hemophilic blood to be that the latter contains less thromboplastin in its plasma.\*

Although most of the complications of hemophilia cannot be controlled except by the transfusion of fresh blood or plasma, an advance has recently been made in the control of bleeding from a local exposed area, such as a tooth socket. This has come out of the investigations of Parfentjev,<sup>58</sup> who by purification of the globulin fraction of rabbit plasmas obtained a substance capable of producing clotting when added in very small amounts to normal plasma or blood. This material was found to act directly on fibrinogen and could clot

prothrombin-free plasma. Parfentjev's results were confirmed by Taylor, Lozner and Adams,<sup>59</sup> who demonstrated that the material was a pseudoglobulin possessing true thrombic activity and differing from thromboplastin. It could be prepared in dry, stable form. Lozner, MacDonald, Finland and Taylor<sup>60</sup> found that one part of dry powdered rabbit thrombin could clot 60,000 parts of 0.25 per cent citrated blood within three seconds, and was of distinct value in the control of hemorrhage from small wounds both in normal subjects and in those with various hemorrhagic diatheses, including hemophilia. It is probable that this material will shortly be commercially available.

Although heparin, which is an anticoagulant, is somewhat outside the scope of this review, one should mention the monograph on this subject by Jorpes<sup>61</sup> and a recent symposium<sup>62</sup> on heparin and thrombosis. Ferguson and Glazko<sup>63</sup> have also contributed a short review.

### *Thrombocytopenic Purpura*

The controversy still continues about whether the bleeding in thrombocytopenic purpura is due solely to a deficiency in the blood platelets or to a vascular factor. MacFarlane,<sup>64</sup> in a comprehensive and critical review of hemostasis, concludes that the platelets, aside from their role as accelerators of blood coagulation and clot retraction, do not have an essential part in the hemostatic mechanism, but that the contractility of the blood-vessel wall is all important. In idiopathic thrombocytopenic purpura, the significance of the platelet count is denied, but the capillaries of the nail bed are very irregular and distorted. These observations hardly agree with the almost instantaneous response to splenectomy and the striking changes of the megakaryocytes in the marrow before and after the operation. Rabinowitz<sup>65</sup> contributes yet another theory, namely, that the liver function in the disease is somehow impaired. The oral administration of an amino acid, methionine, is stated to be effective in controlling the spontaneous bleeding and the defective clot retraction, and to be "of inestimable value in the management of both the acute and chronic stages of the disease." In view of the many substances that have been recommended in the treatment of thrombopenic purpura, the results with methionine must await confirmation. Elliott and Whipple<sup>66</sup> conclude that the role of the spleen in the disease is active and important, although the capillary factor is also of consequence. It should be remembered, however, that the pathognomonic feature of idiopathic thrombopenic purpura is the great reduction in the blood platelets, and that the disease is almost always cured, capillaries or no capillaries, by

\*The work of these three investigators contradicts that of Taylor and his associates which indicates that platelets have little if any relation to the clot-forming globulin substance.



splenectomy, which results in a dramatic and sustained rise in the platelet count.

The exact relation of the spleen to the disorder is not entirely clear, although it is my contention that some sort of functional abnormality develops there and causes an unusual inhibition of platelet formation from megakaryocytes in the bone marrow. This is based chiefly on bone-marrow studies before and after splenectomy. Another method of approach is that of the injection of splenic extracts prepared from splenectomized cases. Troland and Lee<sup>67</sup> reported a remarkable reduction in the platelet count of rabbits when an active extract ("thrombocytopen") was injected. A number of investigators have failed to confirm this apparently clear-cut finding; on the other hand, Rose and Boyer<sup>68</sup> and, more recently, Otenasek and Lee<sup>69</sup> offer complete confirmation in several cases.

What is clear in the disease is the dramatic effect of splenectomy. With a patient bleeding acutely from all the orifices and into the skin, it is first essential to rule out acute leukemia or other disease and at the same time rule in the idiopathic form of thrombopenic purpura. The blood picture does not always permit this differentiation, and for this reason, it is my custom always to perform a sternal puncture. If the marrow shows no evidence of leukemic or other proliferative lesion but presents large numbers of megakaryocytes without platelet formation, immediate splenectomy is recommended, because if the natural procrastination is allowed to win out, a fatal hemorrhage into a vital organ—usually the brain—may well occur. In the past year, I have seen 3 such cases, in which for various reasons the decision for splenectomy was delayed; in the meantime, while the discussion was continuing, the patient in each case had a cerebral hemorrhage and died. In contrast to this, in a recent dramatic case, a young woman had an appendectomy and almost simultaneously began to bleed into the abdominal wound and the skin, and from all the orifices. Despite several transfusions, her condition soon became desperate. There was marked anemia and tachycardia. After study of the blood and marrow indicated an idiopathic thrombopenic purpura, immediate splenectomy was recommended despite the obvious surgical risk and the recent abdominal operation. Splenectomy resulted in quick cure. In this case, the almost 100 per cent mortality with watchful waiting was balanced against the perhaps 30 to 50 per cent mortality of splenectomy.

### Vascular Purpura

Bleeding into the skin or mucous membranes may take place in the presence of normal platelets and under conditions of capillary damage induced by infectious, toxic, allergic or unknown agents. The "devil's pinches" so common in women and the purpura of nephritis and of the Schönlein-Henoch syndrome are of this vascular type. A deficiency in ascorbic acid leads to the capillary hemorrhages so common in scurvy. Vitamin C has been tried for many types of vascular purpura, but it is completely without effect except when a deficiency in that vitamin is present. Recently, vitamin P or citrin (Szent-Györgi) derived from lemon juice or orange peel has been suggested as a regulator of vascular permeability and, hence, as an effective agent in the treatment of vascular purpuras. Kugelmass<sup>70</sup> reported good results with this material in the treatment of 2 cases of allergic purpura, 1 of infectious purpura and 1 of nutritional purpura. In a case of purpura hemorrhagica occurring after arsenic therapy, Gorrie<sup>71</sup> reported quick recovery following treatment with vitamin P (Hesperidin, Glaxo). These results deserve further study before their real value is determined.

113 Bay State Road

### REFERENCES

- 1 Rohr, K. *Das menschliche Knochenmark Seine Anatomie, Physiologie und Pathologie nach Ergebnissen der intravitalen Stereopunktur* 286 pp Leipzig Georg Thieme and Co., 1940
- 2 Morrison, M., and Samwick, A. A. Intramedullary (sternal) transfusion of human bone marrow. preliminary report *J M A* 115:1708 1711, 1940
- 3 Tocantins, L. M., and O'Neill, J. F. Infusion of blood and other fluids into circulation via bone marrow. *Proc Soc Exper. Biol & Med* 45:782, 1940
- 4 Daland G. A., and Worthley, K. The resistance of red blood cells to hemolysis in hypotonic solutions of sodium chloride *J Lab & Clin Med* 20 1122 1136, 1934
- 5 Waugh T. R., and Asherman, E. G. Use of index of hemolysis in expressing fragility of erythrocytes *J Lab & Clin Med* 23 746-751 1938
- 6 Waugh, T. R., and Lamontagne, H. Some observations upon a case of hereditary hemolytic jaundice *Am. J M Sc.* 199:172 181, 1940
- 7 Hunter, F. T. Photoelectric method for quantitative determination of erythrocyte fragility *J. Clin Investigation* 19:691 694, 1940
- 8 Cruz, W. O., Hahn, P. F., Bale, W. F., and Balfour, W. M. Effect of age on susceptibility of erythrocyte to hypotonic salt solution. Radioactive iron as means of tagging red blood cell *Am J M Sc* 202:157 163, 1941
- 9 Gibson, J. G., 2nd. Clinical significance of blood volume *Ann Int Med* 14 2014 2026, 1941
- 10 Miller, E. B., Singer, K., and Dameshek, W. The daily fecal urobilinogen output and the hemolytic index in the measurement of hemolysis *Arch Int Med* (in press)
- 11 Ebert, R. V., and Stead, E. A., Jr. Demonstration that in normal man no reserves of blood are mobilized by exercise, epinephrine and hemorrhage *Am J M Sc* 201:655 664, 1941
- 12 Hahn, P. F., Balfour, W. M., Ross, J. F., Bale W. F. and Whipple, G. H. Red cell volume, circulating and total as determined by radio Fe *Science* 93 87, 1941
- 13 Ivy, A. C., Shapiro, P., and Melnick, P. The bleeding tendency in jaundice *Surg, Gynec & Obst* 60 781 784 1935
- 14 Ivy, A. C., Nelson, D., and Bucher, G. The standardization of certain factors in the cutaneous "venostasis" bleeding time technique *J Lab & Clin Med* 26:1812 1822, 1941
- 15 Landsteiner, K., and Wiener, A. S. An agglutinable factor in human blood recognized by immune sera for Rhesus blood *Proc Soc Exper Biol & Med* 43:223, 1940
- 16 Wiener, A. S., and Peters, H. R. Hemolytic reactions following transfusions of blood of homologous group, with three cases in which the same agglutinin was responsible *Ann Int Med* 13 2306-2322, 1940
- 17 Levine, P., Vogel, P., Katzin, E. M., and Burnham L. Pathogenesis of erythroblastosis fetalis: statistical evidence *Science* 94 371 1941

18. Levine P, Katzin E M, and Burnham L. Isoimmunization in pregnancy its possible bearing on etiology of erythroblastosis foetalis. *J A M A* 116 825-827, 1941
19. Lindheimer K and Wiener A S. Studies on an agglutinin (Rh) in human blood reacting with anti-rhesus sera and with human foetal bodies. *J Exper Med* 74 309-320, 1941
20. Wiener A S and Silverman I J. Subdivisions of group A and group AB, with special reference to so-called agglutinin A<sub>2</sub>. *Am J Clin Path* 11 45-53, 1941
21. Silverman I J. Preparation of anti-M, anti-N, anti-A and anti-B typing fluids. *J Lab & Clin Med* 26 1338-1344, 1941
22. Wiechky E, Klendshoff N, and Swanson P. Preparation and transfusion of safe universal blood. *J A M A* 116 2654-2656, 1941
23. Doan C A and Reinhardt H L. Basophil granulocyte basophilic leukemia and myeloid leukemia basophil and mixed granulocyte types experimental clinical and pathological study, with report of new syndrome. *Am J Clin Path* 11 139, 1941
24. Weis S J, Dolgoplov V B, and Stern M E. Infectious mononucleosis—diagnostic problem. *Am J M Sc* 201:474-483, 1941
25. Thelander H E, and Shaw T B. Infectious mononucleosis with special reference to cerebral complications. *Am J Dis Child* 61:1131-1145, 1941
26. Sadek J F, Jr. Skin eruption and false positive Wassermann in infectious mononucleosis (glandular fever). *Internat Clin* 1:339-345, 1941
27. Smith C H. Infectious lymphocytosis. *Am J Dis Child* 62 231-261, 1941
28. Rinkoff S S, and Spring M. Toxic depression of myeloid elements following therapy with sulfonamides: report of eight cases. *Ann Int Med* 15 89-107, 1941
29. Kennedy P C, and Finland M. Fatal agranulocytosis from sulfathiazole. *J A M A* 116 295, 1941
30. Plum P, and Thomsen S. Agranulocytosis caused by amidoipyridine and by drugs of sulfanilamide group. *Acta med Scandinav* 105 301-311, 1940
31. Lawrence J S. Leukopenia: discussion of its various modes of production. *J A M A* 116 478-484, 1941
32. Muerter R O, Moore L T, Stewart J W, and Brown G O. Chronic granulocytopenia caused by excessive splenic lysis of granulocytes: report of case. *J A M A* 116 2255-2257, 1941
33. Doan C A. The reticulo-endothelial system. In: *Symposium on the Blood and Blood Forming Organs*. 264 pp. Madison University of Wisconsin Press, 1940. Pp 167-193
34. Dameshek W. The spleen facts and fancies. *Bull New Eng Med Soc* 3 304-311, 1941
35. Schwarz E, and Telesky L. Some facts and reflection on problem of poisoning by benzene and its homologs. *J Indust Hyg & Toxicol* 23 119-194, 1941
36. Goldwater, L J. Disturbances in blood following exposure to benzol. *J Lab & Clin Med* 26 957-973, 1941
37. Goldwater, L J, and Tewksbury M P. Recovery following exposure to benzene (benzol). *J Indust Hyg & Toxicol* 23 217-231, 1941
38. Hamilton Patterson, J L. Chronic benzene poisoning. *Lancet* 1 73-76, 1941
39. Hunter F T. Chronic exposure to benzene (benzol). II. Clinical effects. *J Indust Hyg & Toxicol* 21 331-354, 1939
40. Mallory T B, Gall E A, and Brickley W J. Chronic exposure to benzene (benzol). III. Pathologic results. *J Indust Hyg & Toxicol* 21 355-393, 1939
41. Rayson R, Parker, F Jr and Jackson H, Jr. Industrial solvents as possible etiologic agents in myeloid metaplasia. *Science* 93 541, 1941
42. Davis J E. Production of experimental polycythemia in dogs rabbits and man by daily administration of ephedrine and by amphetamine in dogs. *Am J Physiol* 134 219-224, 1941
43. Altschule M D, Folk M C, and Henstell H H. Cardiac and respiratory function at rest in patients with uncomplicated polycythemia vera. *Am J M Sc* 200 478-483, 1940
44. Dameshek W. Hematology. *New Eng J Med* 224 741-741, 1941
45. Jackson H Jr, Parker, F Jr and Lemon H M. Agnogenic myeloid metaplasia of spleen syndrome simulating other more definite hematologic disorders. *New Eng J Med* 222 985-994, 1940
46. Dameshek W and Henstell H H. Diagnosis of polycythemia. *Ann Int Med* 13 1370-1387, 1940
47. Falconer C A. Treatment of polycythemia. *J A M A* (in press)
48. Lawrence J H. Nuclear physics and therapy: preliminary report on new method for treatment of leukemia and polycythemia. *Radiology* 35 51-64, 1940
49. Perlman L and Fox T A. Hemorrhagic diatheses: analysis of three hundred and fifty five autopsy reports. *Arch Int Med* 63 112-120, 1941
50. Quick A J. Classification of hemorrhagic diseases due to defects in coagulation mechanism of blood based on recently published studies. *Am J M Sc* 199 118-132, 1940
51. Ferguson J H. Role of blood clotting anomalies in hemorrhagic diseases. *J Lab & Clin Med* 26 52-64, 1941
52. Valentine E H, Reinhold I G, and Schneider E. Effectiveness of prenatal administration of 2-methyl-1,4-naphthoquinone in maintaining normal prothrombin levels in infants. *Am J M Sc* 202 359-364, 1941
53. Lucas S P, and Aggeler P M. Influence of liver damage on plasma prothrombin concentration and response to vitamin K. *Am J M Sc* 201 327-340, 1940
54. Lord J W Jr and Andrus W DeW. Differentiation of intrahepatic and extrahepatic jaundice: response of the plasma prothrombin to intramuscular injection of menadiolone (2-methyl-1,4-naphthoquinone) as a diagnostic aid. *Arch Int Med* 26 199-210, 1941
55. Bincham J B, Meyer, O O and Poble F J. Studies on the hemorrhagic agent 3,3-methylenebis(4-hydroxycoumarin). I. Its effect on the prothrombin and coagulation time of the blood of dogs and humans. *Am J M Sc* 202 563-578, 1941
56. Quick A J. Diagnosis of hemophilia. *Am J M Sc* 201 469-474, 1941
57. Howell W H. Recent advances in problem of blood coagulation applicable to medicine. *J A M A* 117 1059-1062, 1941
58. Tannenbaum I A. A globulin fraction in rabbit plasma possessing a strong clotting property. *Am J M Sc* 202 578-584, 1941
59. Taylor F H L, Lerner E L, and Adams M A. The thrombotic activity of a globulin fraction derived from rabbit plasma. *Am J M Sc* 202 585-592, 1941
60. Lerner E L, MacDonald H, Finland M, and Taylor F H L. The use of rabbit thrombin as a local hemostatic. *Am J M Sc* 202 593-598, 1941
61. Jorpes J E. *Heparin: its chemistry, physiology and application in medicine*. 87 pp. New York: Oxford University Press, 1939
62. Symposium on heparin. *Acta med Scandinav* 107:107-178, 1941
63. Ferguson J H and Glazko A J. Heparin. *J Lab & Clin Med* 26 1559-1564, 1941
64. MacFarlane R G. Critical review: Mechanism of haemostasis. *Quart J Med* 10 1-29, 1941
65. Rabinowitz H M. Study of role of amino acids in clot retraction: effect of methionine in restoring normal clot retraction and control of bleeding in essential thrombocytopenic purpura. *Am J Surg* 51 366-378, 1941
66. Elliott P H E Jr and Whipple M A. Observations on interrelationship of capillary platelet and spleen factors in thrombocytopenic purpura. *J Lab & Clin Med* 26 489-498, 1940
67. Troland C E and Lee F C. Thrombocytopenic substance in extract from spleen of patients with idiopathic thrombocytopenic purpura that reduces number of blood platelets. *J M A* 111 221-226, 1938
68. Rose H Jr and Boyer L B. Thrombocytopenic confirmatory report. *J Clin Investigation* 20 81-86, 1941
69. Oienstein F, and Lee F C. Further observations on thrombocytopenic. *J Lab & Clin Med* 12 166-173, 1941
70. Kugelmas I N. Vitamin P in vascular purpura. *J A M A* 115 519, 1940
71. Gorrie D R. Purpura haemorrhagica after arsenic therapy treated with vitamin P. *Lancet* 1 100-100, 1940

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTE-MORTEM AND POST-MORTEM RECORDS AS USED  
IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

### CASE 28101

#### PRESENTATION OF CASE\*

A twenty-three-month-old Portuguese-American girl was admitted to the hospital because of dark-colored urine.

One week before entry, she began to void dark urine and to pass light-colored stools. For two days previous to entry, she was feverish, and it was noted that the abdomen was enlarged. She had no vomiting, diarrhea or other systemic or constitutional symptoms.

The family history was not contributory. The patient was a full-term, normally delivered infant who had received an adequate diet and had undergone normal growth and development.

Physical examination revealed a well-developed and well-nourished child whose breathing was rapid and shallow, but regular. There was moderate icterus of the skin and scleras. Shotty lymph nodes were palpable bilaterally in the cervical and inguinal regions. The heart and lungs were normal. The abdomen was protuberant and tense. The liver edge was palpable at the level of the umbilicus. There was no spasm or tenderness. The spleen and kidneys were not palpable, and no fluid wave was obtained. Examination of the nervous system was negative.

The temperature was 99.6°F., the pulse 140, and the respirations 28.

Several samples of urine were deep brown, with moderate amounts of bile. There were slight traces of albumin on several occasions, with repeatedly negative sediments. The urine was free of urobilinogen. Examination of the blood showed a red-cell count varying between 3,560,000 and 5,100,000 with corresponding hemoglobin determinations between 69 and 83 per cent, and white-cell counts ranging between 13,000 and 19,000 with a normal differential. The blood Hinton reaction was negative. Repeated blood cultures were negative. The venous clotting time was 7 minutes, with a normal clot retraction. The fasting blood sugar was 182 mg. per 100 cc., and the blood cholesterol 268 mg. The van den Bergh reaction was biphasic,

and the nonprotein nitrogen of the blood serum was 28.7 mg. per 100 cc. The stools were constantly clay colored. Repeated brucellergin tests and tuberculin tests in dilutions up to 1:10 were negative. Investigation of the sputum for fungi was negative.

Roentgenograms of the skull and extremities were negative, and those of the lungs showed a moderate amount of diffuse, fine, mottled peribronchial infiltration. On repeated examinations of the chest, the infiltration became more diffuse over a two-week period and then remained unchanged until three months later, when the lung fields became more vesicular and emphysematous.

The patient remained in the hospital for four months. During this time, she ran an intermittent low-grade temperature, with occasional bouts of fever up to 103°F. Her condition remained essentially unchanged except for a slight but steadily progressive loss of weight. Jaundice persisted. Two and a half weeks after entry, the spleen became palpable. Three and a half months after entry, a lymph-node biopsy was interpreted as showing chronic nonspecific lymphadenitis. Four months after admission, an exploratory laparotomy was performed. Although the patient apparently withstood the procedure quite well, death occurred on the first postoperative day.

#### DIFFERENTIAL DIAGNOSIS

DR. HARRY L. MUELLER: We might pause for a moment to remark that this is a Portuguese infant and that the onset of the jaundice may therefore have been at an earlier date than was suspected, because these children are rather apt to have dark, olive skins.

This patient was in the hospital for four months. If she had a progressive constitutional disease, it is surprising that her condition did not become much worse during that period than is apparent from this history.

Painless, persistent jaundice, with clay-colored stools, and the large liver persisting for four months in a two-year-old infant certainly make me believe that there was some unusual cause of obstruction to the biliary drainage system. The fact that the child exhibited no gastrointestinal symptoms at an age when almost any disease is accompanied by such symptoms makes me quite confident that there was no disease in the gastrointestinal tract. I am ruling out catarrhal jaundice, which is the common cause of jaundice in a child, although quite rare at this age, because of the long course and the fact that there were no gastrointestinal symptoms.

We must assume a point of obstruction and select

\*This case is presented through the courtesy of the Children's Hospital, Boston.

the most likely point and cause for that obstruction. I should consider the portal fissure the most probable position, and it appeals to me to place Hodgkin's disease in that region. The loss of weight, fever, pulmonary lesion and apparently normal blood picture, as well as the later development of splenic enlargement, are all consistent with Hodgkin's disease. This condition may present an apparently normal blood picture, occasionally has a leukocytosis, and may have a relative lymphocytosis, which might explain why the differential count appeared normal, although there was a leukocytosis. The negative biopsy does not to my mind rule out Hodgkin's disease. Another lesion that should be given serious consideration is lymphosarcoma in the same region, although the course of the disease does not fit in so well. Lymphosarcoma is prone to metastasize to both the bronchial and the mediastinal lymph nodes, and such metastasis must be considered. Tuberculosis in this position does not often cause pressure symptoms, and with a negative tuberculin reaction and the lack of any report of calcification I should be inclined to rule that out. We might stop here and get an interpretation of the x-ray films.

DR. AUBREY O. HAMPTON: This is a very unusual pulmonary picture. In the first examination, it looks very much like miliary tuberculosis. In fact, that would be my unhesitating opinion if I saw this film alone. I should think that it was in the terminal stage and that the patient would die much sooner than in three months—in fact, three days would be more likely. However, the pulmonary picture changes markedly in three months and shifts into something entirely different. At first, there was a miliary process in the lung, and at the last examination there is what appears to be pulmonary fibrosis with emphysema. I have not seen pulmonary fibrosis that started out as a miliary lesion. In some respects, the progression is like silicosis, which can begin with a miliary lesion, and later shifts into extreme fibrosis with blebs, but a child does not have silicosis. The marked increase in the anteroposterior diameter of the chest is like emphysema. The abdomen is rather unusual. Here is the shadow of what appears to be the liver. It is unusually distinct in the lateral view; it is not so distinct in the anteroposterior view, but it is certainly enlarged. I think that the spleen is represented here—moderately enlarged, not markedly. That film was taken four months before death.

DR. MUELLER: Can you make out any kidney shadows?

DR. HAMPTON: The right kidney appears normal in size and shape. I do not see the left.

DR. MUELLER: Is there any question of a retroperitoneal mass?

DR. HAMPTON: No; and I do not believe that lymphoma would produce this chest picture unless a great deal of radiation had been given.

DR. MUELLER: Could Hodgkin's disease regress as the result of frequent x-ray and fluoroscopic studies?

DR. HAMPTON: This is a very diffuse lesion. All the lobes are involved alike. I do not believe we could produce that picture with radiation if we tried.

DR. MUELLER: Is there any evidence of enlargement or calcification of the mediastinal lymph nodes?

DR. HAMPTON: No.

DR. MUELLER: I do not know much more than I did before we started except that I am a little more confused. I am convinced that this child had an obstructing lesion somewhere in the biliary drainage system. We must try to couple it with the pulmonary process and decide whether the primary lesion was in the lungs or in the abdomen.

Malignant tumors in infants of this age have a very rapid course, and I do not believe that the child would have been in such good condition at the end of four months if the metastases had been so widely distributed. There is also no evidence of a palpable mass, although that could be tucked up under the edge of the liver. Stone seems very unlikely, with the other aspects of the case, and of course is rare in a child of this age. I do not believe we have to consider it seriously. Foreign body should always be considered in children. Any foreign body that would obstruct the biliary tract would certainly cause some gastrointestinal symptoms. Parasites should perhaps be more seriously considered than I had thought previously. Distoma and ascaris can both invade the common and intrahepatic ducts, as well as the cystic, and can cause obstruction. I should expect stool examinations to pick up some evidence of that. There is nothing in the record to show that the stool examinations were made with that in mind. One other parasite that ought to be considered is the hydatid cyst. The Portuguese are sheep herders. There is no mention in the record that these people had a sheep dog, but a hydatid cyst impinging on the hepatic duct could give a course similar to this. What type of lesion might result in the lungs from ruptured hydatid cyst, I am frank to say I do not know, but I do not believe that has to be considered seriously. Tumors of the pancreas and gastrointestinal tract and kidney are rather unlikely because they would present other gastrointestinal or urinary signs and symp-

toms, none of which were present in the entire course. Wilms's tumor must always be considered in a child and on the right side can cause obstruction of the biliary tract. It metastasizes early, and I doubt whether it can present such a picture as this in the lungs. It also metastasizes to bones, and x-ray films of the long bones were negative. Primary tumor of the liver itself seems unlikely. The liver was smooth; it showed no irregularities, and these tumors grow very rapidly and I believe would present other evidence of cancer in the patient.

Turning to the question of infection, syphilis should be considered. Against it are the negative blood Hinton reaction and the absence of changes in the long bone and of other stigmas. Brucella and fungous infections, which have been quite well ruled out by the clinicians, would not present persistent obstructive jaundice with clay-colored stools for that period. Liver abscess is, I think, a greater possibility than I originally considered. It possibly could be the source of multiple septic foci in the lung. It would be unusual for such foci to become fibrosed as these did, but this is an unusual case and we must consider every possibility. Abscess can run a fairly silent course in the liver itself and be very difficult to diagnose and sometimes, is diagnosed only by its metastatic lesions. Congenital anomalies are always a source of worry to the pediatrician. Liver cysts, cysts of the biliary ducts and stenosis of the ducts could cause half this picture but not, I believe, the complicated picture in the lung.

I come back to my original thought that, to make a diagnosis in this case, an exploratory laparotomy would probably have been necessary, and whether it was done for that reason I do not know. I should say that this child had obstructive jaundice. I do not know to what the lesions in the lungs are due. I had picked as my first choice Hodgkin's disease, but with this picture in the lungs I tend more to favor infection and should say liver abscess or localized infection in the portal fissure. I should also like to put in a guess, because of the patient's nationality, that there is a possibility of a hydatid cyst.

DR. TRACY B. MALLORY: Dr. Hampton, would you be willing to make a diagnosis?

DR. HAMPTON: No; I have not the vaguest idea. I should like to know whether an oil spray was used. It could produce that picture in the lungs.

#### CLINICAL DIAGNOSES

Biliary cirrhosis, obstructive.

Pulmonary fibrosis, chronic, nonspecific.

#### DR. MUELLER'S DIAGNOSES

Obstructive jaundice.

Liver abscess?

Hodgkin's disease?

Hydatid cyst?

#### ANATOMICAL DIAGNOSIS

Hand-Schueller-Christian syndrome, with involvement of liver, lungs, lymph nodes, bone and so forth causing interstitial emphysema (marked) and obstructive biliary cirrhosis.

#### PATHOLOGICAL DISCUSSION

DR. SIDNEY FARBER\*: The clinical diagnoses were obstructive biliary cirrhosis and chronic, non-specific pulmonary fibrosis. The exact nature of the disease was not understood by the clinicians during the life of the child, and nothing was learned from the clinical studies. As Dr. Mueller pointed out in the clinical history, the child was not malnourished and was really more unhappy than desperately ill throughout most of the course.

At autopsy, a granulomatous process that involved many parts of the body but mainly the lungs, the lymph nodes, the liver and the bone marrow, and also the kidney, uterus and tongue, was found. There was an obstructive biliary cirrhosis secondary in part to pressure on the common duct caused by enlarged lymph nodes and a mass of granulation tissue, and in part to compression of the intrahepatic bile ducts by masses of granulation tissue and granulomatous involvement of the liver parenchyma. A considerable amount of fibrous-tissue replacement of destroyed liver parenchyma was present throughout the liver. The greater amount of obstruction was caused by pressure on the common duct. The extraordinary x-ray picture of the lungs was caused by diffuse destruction of the alveolar walls and infiltration of the interstitial tissues of the lungs by the same type of granulomatous process observed in the extrahepatic lymph nodes and in the liver. Secondary to the destruction of alveolar walls, an escape of air into the interstices of the lung occurred, causing numerous small blebs and pseudocysts widely scattered throughout all lobes of both lungs. Histologically, the granulomatous process in the various parts of the body was characterized by the presence of large mononuclear cells, the cytoplasm containing large or small droplets of lipid or cellular debris, varying degrees of fibrosis and a cellular reaction composed of lymphocytes, occasional plasma cells and, in rare places where necrosis was present, polymorphonuclear

\*Assistant professor of pathology, Harvard Medical School; pathologist, Children's Hospital.

clear leukocytes. The lipid material in the large mononuclear cells stained readily by the scharlach R method, and some of the lipid was definitely doubly refractile.

The exact cause of this granulomatous process is unknown, and no further evidence of etiologic value was obtained from this post-mortem examination. Material from the lung and from the liver was injected by a variety of methods into a number of laboratory animals without the production of any lesion. Bacteriologic study of the heart's blood and tissue from the liver and spleen by aerobic, anaerobic and partial tension methods revealed no growth. The gross and histologic findings were consistent with what has been described as one variant of the Hand-Schueller-Christian disease, and what some writers have called Letterer-Siwe disease. Some patients with lung changes of the same type as those described here have had, in addition, numerous small skin lesions, which are often taken for tuberculides. Some of these patients have had destructive lesions of the skull or other parts of the skeleton. The clinical picture is often obscured by the peculiar localization of the pathologic process. In this patient, the icterus was the most significant part of the clinical picture and is explained mainly by accidental obstruction to the outflow of bile by involvement of the extrahepatic lymph nodes. Some patients have severe destruction of the petrous portion of the temporal bone. After operation, a foul purulent exudate, which may persist for weeks or months, may be found, bacterial infection being of only secondary importance.

A study of material obtained at operation and at autopsy of patients of the type under discussion and from patients with less dramatic visceral involvement, or with lesions limited apparently to the skeleton, has forced me to adopt a working hypothesis that Hand-Schueller-Christian disease, Letterer-Siwe disease and the condition that has come to be known in the last year or two as eosinophilic granuloma of bone or solitary granuloma of bone are all variants of the same disease. Certainly, it is generally recognized that the classical Hand-Schueller-Christian triad of exophthalmos, diabetes insipidus and skeletal involvement represents but one manifestation of the basic pathologic process. The disease appears to be a self-limiting granuloma. Of greatest consequence in the prognosis is the anatomic localization of the lesions.

A. PHYSICIAN: Are the lesions radiosensitive?

Dr. FARBER: Yes; we have not had very much experience, but we have learned that the bone lesions particularly are extraordinarily radiosensi-

tive. At this time, we have a patient on the wards of the Children's Hospital with liver involvement similar to that of the patient under discussion today. The liver is receiving radiation therapy.

A. PHYSICIAN: Why did they operate?

Dr. FARBER: The operation was performed in part to relieve biliary obstruction, if possible, and in part to find out the nature of the pathologic process.

## CASE 28102

### PRESENTATION OF CASE

An eleven-year-old schoolboy, apparently in good health, while playing vigorously outdoors suddenly fell unconscious, took a few breaths and died. A slight sanguineous oozing appeared from the mouth.

At birth, the patient had been delivered at term by forceps but appeared to be well. During his first year, he had presented a difficult feeding problem. At the age of two years, he had a moderately severe upper respiratory infection; at four, he had an attack of unexplained high fever for a few days culminating in a convulsion and recovery.

At five years of age, he had a severe illness that began as a bowel upset with eight to nine movements a day and a little mucus in the stools. The family physician noted for the first time slight cardiac enlargement, a rather rapid rate and a slight apical systolic murmur. There was no fever, rash, epistaxis or joint pains. In two or three days, the bowel irregularity subsided, but the heart action continued overactive without obvious cause. The patient remained quietly at home. Two weeks later, he awoke at midnight complaining of abdominal pain. He was taken to another hospital, where he was found to have a normal temperature. He was pale but not cyanotic. The respirations were rapid. There was considerable puffiness of the face and hands, and slight pitting of the lower legs. The throat was normal, and the lungs were clear. The cervical veins were swollen and pulsating, and the liver was large and very tender and extended to the umbilicus.

The heart was considerably enlarged, rapid and regular at 140. The most striking auscultatory finding was a marked gallop rhythm. There was also a soft apical systolic murmur, which later was inconstant from day to day and ultimately disappeared.

The urine was normal on several examinations. The blood showed a red-cell count of 4,700,000 with a hemoglobin of 94 per cent, and a white-cell count of 7600 with a normal differential count and smear.

An electrocardiogram showed a sinus tachycardia at 130 to 140, and moderate left-axis deviation. The T waves were low in all leads and flat in Lead 1. The P waves were rather high. The PR interval measured 0.17 second.

An x-ray film showed generalized enlargement of the heart both to the right and to the left, without characteristic shape. The transverse diameter was 11.3 cm., and the internal diameter of the chest 18.8 cm. The lungs were normal.

In the hospital, the patient was given 5 gr. of digitalis the first day, 8 gr. the second day, and 4½ gr. the third day, resulting in a striking slowing of the rate from 140 to 100 and a consequent marked improvement in the clinical picture—namely, a brisk diuresis, improvement in the quality of the heart sounds and a lessening in the intensity of the gallop to the order of a moderately loud third sound. No murmur was then audible. The peripheral edema disappeared in three or four days, and after ten days the liver receded to the costal margin. Two later x-ray films showed no significant change in heart size, and three subsequent electrocardiograms showed slightly less left-axis deviation than that on admission but otherwise remained unchanged, including the PR interval. The patient was discharged after a month of hospitalization on a daily ration of ¾ gr. of digitalis.

During the next six years, up to his sudden death, the patient remained in good health, grew normally, and was precocious mentally. His activities were essentially normal for a boy of his age. He was followed by his physicians about twice a year, and at times there was a tendency to mild tachycardia. On these occasions, the gallop rhythm reappeared but subsided with rest and slight increases in the digitalis ration. The heart remained enlarged.

Two years before death,—because of vague abdominal discomfort,—a gastrointestinal series was done in this hospital. The first portion of the duodenum showed a redundant loop crossed by a pressure defect. This deformity, which could be obliterated by manipulation, suggested to the roentgenologist an anatomic variation of the duodenum caused by an aberrant mesenteric artery.

One month before death, at the time of a routine checkup, the patient was well except for a slight respiratory infection. There was no cyanosis or clubbing and no palpable liver or spleen. There was a slight prominence of the left chest anteriorly. The cardiac apex was visible in the fifth interspace 8 cm. from the midsternal line and 2 cm. outside the midclavicular line. The action was quiet and regular at 80. There were no murmurs.

In the recumbent position, there was a slight third sound. The blood pressure was 95 systolic, 65 diastolic. Under the fluoroscope, the heart was moderately enlarged and globular in shape. The transverse diameter was 11.6 cm., and the internal diameter of the chest 19.5 cm. The lungs were normal. An electrocardiogram showed moderate to marked left-axis deviation and a PR interval of 0.20 second. The T waves in Lead 1 were inverted, and the P waves were slightly prominent. It was thought that the patient was doing well.

#### DIFFERENTIAL DIAGNOSIS

DR. PAUL D. WHITE: If this eleven-year-old boy had heart disease,—and his end sounds like a cardiac death, since most cerebral deaths are not so speedy,—the kind should be, in the order of probability, rheumatic, congenital or (quite possibly in the present case) something else. If it was either rheumatic or congenital, it was a rare case.

I cannot make much of these first events in the past history in view of what followed. Rheumatic fever generally does not take the course of a high fever culminating in a convulsion.

Almost any illness at the age of five may, however, excite acute active rheumatic heart disease, and it is possible that the sickness at that time induced the first manifestation of rheumatic or rheumatic-like heart disease with cardiac enlargement and rapid heart rate. From the intestinal trouble, I tried to work in some parasitic myocardial disease beginning during this illness, but I was unable to do so.

We do not know just how severe the abdominal pain was, except that it was severe enough to wake the patient up. One wonders if it was a complication associated with heart failure, such as liver engorgement. Pericarditis, dry or with effusion, sometimes gives rise to epigastric pain.

The patient had been flat in bed, so that this generalized edema may have been either cardiac or renal. So far as the cardiac examination is concerned, the edema might have been secondary to pericardial effusion, or it might more likely have been due to congestive heart failure. One hears a gallop rhythm frequently in constrictive pericarditis, but not in cases of acute pericarditis with effusion. The gallop rhythm is, however, much more in favor of cardiac dilatation. It can be induced by heart block alone, with long PR intervals in the electrocardiogram; the auricular contraction can then be heard.

Was the blood pressure noted at that time?

DR. EDWARD F. BLAND: It was essentially the same as it was later on.

Dr WHITE: The fact that the urine was normal on several occasions is important. We do know that at this age an acute nephritis may be associated, as Dr. Longcope and others have shown, with cardiac dilatation and often with failure that may take months to clear up.

The left-axis deviation is suggestive of something unusual at five, for even when of moderate degree it is rare at this age. The low T waves were abnormal and fit in with pericardial or myocardial disease, leaving out, of course, a state of myxedema or some other rare factor that would be very unlikely in this boy. The PR interval was rather long, but not excessively so.

Are there any x-ray films?

Dr AUDREY O HAMPTON: This film was taken six years before death. There was not much change in later examinations.

Dr WHITE: This film shows generalized enlargement of the heart. The shadow is rather globular and not diagnostic, so far as I know, of any one condition. There is, of course, so called "idiopathic cardiac hypertrophy," congenital or not, in young children, which usually does not allow survival to this age. The x-ray picture is sometimes like this one. Such cases are, however, being subdivided, and an ample cause for the hypertrophy is usually found.

Dr HAMPTON: Do you want to explain why the left main bronchus is elevated? I think it is an unusual finding for almost any type of heart disease unaccompanied by left auricular enlargement.

Dr WHITE: Enlargement of the left auricle is certainly the usual cause for such a blunt-angled bifurcation of the trachea, and yet there is no particular reason to think that the left auricle was predominantly enlarged in the present case. I do not know that I have seen it in congenital enlargement of the heart. We have, however, no oblique view to indicate the presence or absence of some enlargement of the left auricle.

The patient was able to tolerate a good deal of digitalis—most children can. The result was an excellent classic digitalis effect in the presence of normal rhythm. Undoubtedly, the digitalis was responsible for the improvement in this case. He apparently continued with digitalis throughout the rest of his life. Is that true, Dr. Bland?

Dr BLAND: That is correct.

Dr WHITE: "No murmur was then audible" This is unusual in the presence of rheumatic heart disease because even dilatation, which may persist, results in most cases in a permanent murmur or murmurs, whether the valves are deformed or not.

The patient left the hospital, to remain away for six years, in a fair state of health, except for one interval. He was, however, really a patient for those six years, not a hale and hearty, strong boy. The myocardial reserve seems to have been distinctly limited.

The aberrant mesenteric artery is very intriguing. It may be a clue to anomalies elsewhere.

The absence of cyanosis and clubbing rules out quite definitely the cyanotic type of congenital heart disease. Rarely, the tetralogy of Fallot may be associated with only slight cyanosis, but I do not believe that we can consider the usual causes for the cyanotic type of congenital heart disease in this case.

The slight prominence of the left chest anteriorly is due, I suppose, to the marked enlargement of the heart during growth, which forced the chest wall forward.

Did the fluoroscopic examination show the same findings as the earlier x-ray film?

Dr HAMPTON: Yes; both recorded a transverse diameter of about 11 cm.

Dr WHITE: The heart had not grown rapidly larger. That is, it stayed large without great change all those six years, while the body was growing. Digitalis may have helped to maintain fairly good myocardial tone and thus may have prevented greater enlargement.

This electrocardiogram might be the record of a very large heart, with hypertrophy predominantly of the left ventricle. Inversion of T waves does not necessarily mean coronary artery disease. A large left ventricle, with or without coronary disease, may produce this picture.

The death sounds like that due to coronary insufficiency. As I said in the beginning, the diagnosis must be heart disease of either rheumatic, congenital or unknown cause, and so far as I can make any positive diagnosis, it must be labeled "unknown." But I shall make an attempt. It is obvious that the patient had a large heart, particularly involving the left ventricle. There is no reason to doubt that. Whether the left auricle was large and what the other heart chambers may have shown, I do not know. I suspect that the heart was enlarged throughout, though in the left ventricle predominantly.

There was no evidence of hypertension, either systemic or pulmonary, and no evidence of valvular defect. There was myocardial disease, I think, of some sort—what kind, I cannot determine. Was it rheumatic without valvular disease? I wonder if enlarged hearts of unknown origin that we encounter in rare cases in adult life may



not be rheumatic after all, even in the absence of a positive rheumatic history or of any valvular deformity, left over from an insidious rheumatic infection involving the myocardium alone in childhood. There probably are a few of these cases, but of course we cannot prove them. And they are not common. Or this child's heart disease may have come directly from the sudden severe and obscure intestinal illness; we are, however, not acquainted with that kind of heart disease, if it exists. The patient had not had diphtheria. The electrocardiogram did not resemble such an effect. Was it toxic poisoning of unknown nature? Or was it a congenital anomaly of the blood supply? I am intrigued by that idea. This patient is rather old for it, and yet in France during the last war, in 1916, I attended the autopsy of a young soldier with an anomalous coronary circulation. His death was sudden, and we thought that it was probably due to an insufficient coronary blood supply. Consequently one can live to the age of eleven and beyond and die suddenly with an anomalous coronary blood supply. In the very striking case that we had in this hospital several years ago, the patient did not survive longer than a few months after birth. That patient had a left coronary artery that arose from the pulmonary artery and supplied the left ventricle with venous blood. We thought that, despite his age, he had angina pectoris. The electrocardiogram showed inversion of the T waves in Lead I. Later, we found the congenital anomaly and a very large heart with extensive myocardial degeneration throughout the left ventricle. Perhaps the aberrant mesenteric artery is a clue to anomalous circulation elsewhere. Could this have been von Gierke's, that is, glycogen-storage, disease? The boy was distinctly old for it, but I do not know what the oldest case on record is. The lesion might, I suppose, have been rhabdomyoma, which I know very little about except that most patients do not survive nearly to this age; most of them die within a few months after birth.

I shall guess one of the bizarre diagnoses this time; perhaps a more likely one might be rheumatic or unknown heart disease, but I favor a congenital anomaly and put my first bet on anomalous coronary blood supply and my next on von Gierke's disease; a remote possibility is some tumor such as a rhabdomyoma. My second choice as to type is rheumatic heart disease of very unusual form, and my last choice is something else that may well have been the answer that I may not even have mentioned.

DR. BLAND: I first saw this boy during his severe illness six years ago at the Children's Hospital at the request of the late Dr. Kenneth Blackfan. We were much impressed by his rapid im-

provement on digitalis; so much so that we accepted it as clinical evidence against a serious myocarditis on an infectious basis, such as rheumatic, diphtheritic or secondary to acute nephritis. Thereafter, the patient lived a fairly normal and very active life. He was closely followed because of our special interest in what we considered a most unusual form of heart disease and also because of his parents' natural apprehension about his future.

The only other comment I should like to make is that I was intrigued by Dr. Hampton's suggestion two years before the patient died that he had an aberrant mesenteric artery, because it gave some support to Dr. Blackfan's and my opinion that this was a congenital idiopathic hypertrophy of the heart. I do not know the exact explanation for the unexpected death.

DR. HOWARD B. SPRAGUE: I suppose that the patient might have had a three-chambered heart. The electrocardiogram is not like that in our series of one case, but it is a possibility.

#### CLINICAL DIAGNOSES

Congenital idiopathic hypertrophy of the heart.  
Aberrant vessel in region of duodenum.

#### DR. WHITE'S DIAGNOSES

Marked cardiac enlargement, of unknown cause.  
Congenital anomaly of the coronary circulation?  
Von Gierke's (glycogen-storage) disease??  
Rheumatic heart disease, without valvular deformity???

#### ANATOMICAL DIAGNOSIS

Hypertrophy of the heart, cause unknown.

#### PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: This is the type of case in which the Pathology Department has to confess complete failure too. This patient had a very large heart—240 gm.; the estimated normal size for a boy of his age would be around 112 gm. This was twice the normal size. All the chambers of the heart took part in the dilatation and hypertrophy quite uniformly, with no evidence of preponderance in either side. Besides hypertrophy, the only definite finding was a generalized thickening of the endocardium, notable in both ventricles and even a little more marked in the left auricle. The mitral valve showed two or three spots of fibrous thickening that did not suggest rheumatic endocarditis. The chordae tendineae were not in the least thickened or short, and there was no interadherence of the leaflets. Microscopically, there was no valvulitis. We cut a great many sections of different portions of the

myocardium, and there was no fibrosis and nothing to suggest an Aschoff nodule or any arterial involvement. The coronary arteries were normal in size and location. The aberrant artery, which Dr. Hampton suggested, was found crossing the duodenum. There was an azygos lobe of the lung. Possibly, these two things could be interpreted as evidence of congenital defect, and we can call this congenital hypertrophy. I know no way of settling the matter. I can simply make a diagnosis of hypertrophy of the heart, cause unknown.

DR. WHITE: On further review of this case, I believe it unwise to label it as an example of "congenital idiopathic hypertrophy" of the heart.

There certainly was hypertrophy, with a history of congestive failure and a cardiac death, but there was no evidence of any heart trouble until the severe illness at five. To my mind, that illness in some manner, toxic or otherwise, which we do not understand, quite probably injured the heart. In view of the intestinal symptoms and fever during the severe acute illness at the age of five, when the heart trouble seemed to begin, it has been suggested that an acute trichinous invasion of the body may have set off the heart trouble.

DR. MALLORY: I think in that case we should have found encysted trichinae, since once encysted they never disappear.

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established in 1828

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND  
PUBLISHED UNDER THE JURISDICTION OF THE  
COMMITTEE ON PUBLICATIONS

Official Organ of  
THE MASSACHUSETTS MEDICAL SOCIETY  
and  
THE NEW HAMPSHIRE MEDICAL SOCIETY

EDITORIAL BOARD

Joseph Garland, M.D.	Stephen Rushmore, M.D.
William B. Breed, M.D.	Henry R. Viets, M.D.
George R. Minot, M.D.	Robert M. Green, M.D.
Frank H. Lahey, M.D.	Charles C. Lund, M.D.
Shields Warren, M.D.	John F. Fulton, M.D.
George L. Tobey, Jr., M.D.	A. Warren Stearns, M.D.
C. Guy Lane, M.D.	Dwight O'Hara, M.D.
William A. Rogers, M.D.	Chester S. Keefer, M.D.

ASSOCIATE EDITORS

Thomas H. Lanman, M.D.      Donald Munro, M.D.  
Henry Jackson, Jr., M.D.

Walter P. Bowers, M.D., EDITOR EMERITUS  
Robert N. Nye, M.D., MANAGING EDITOR  
Clara D. Davies, ASSISTANT EDITOR

SUBSCRIPTION TERMS: \$6.00 per year in advance, postage paid, for the United States (medical students, \$3.50 per year); Canada, \$7.04 per year, Boston funds; \$8.52 per year for all foreign countries belonging to the Postal Union.

MATERIAL for early publication should be received not later than noon on Friday.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston, Massachusetts.

## "THE AMERICAN WAY OF LIFE"

PHRASES play an important part in shaping the decisions of our national life, as they flash through the minds of men and women and strike fire from their imaginations. They help to constitute the emotional propaganda by which we form our judgments and see more clearly, or so we hope, the differences between right and wrong.

In 1917, American youth took the eastward passage to "make the world safe for democracy," and if there is too much uncertainty concerning the idealism of the movement, let the doubter see the panels painted by John Singer Sargent in the Widener Library at Cambridge. In 1942, we find ourselves having again accepted the challenge,

that in this world of chaos we may preserve "the American way of life."

What is this way of life, of which we are so proud when we find it threatened? Let us call it the opportunity that we, as a people, have seized and preserved of determining our own national destiny and of maintaining certain constitutional rights of the individual. We may not have planned our destiny well or pursued it with vigor, and we may have saddled ourselves with a government by bureaus; but we have done so of our own free will, through our elected representatives, and we still have the power to change it all, should we decide that there is a need.

In the last decade, our freedom has been jeopardized by forces that have required extraordinary opposing measures. Our economic structure has failed us to the point where we have been willing to accept an unbelievable amount of restriction in our daily activities, and in the midst of this depression, in 1931, a wave of aggression was started by totalitarian nations that we, and their other democratic neighbors, lacked the courage to stop.

When military aggression finally assumed epidemic proportions, we became aware of our own danger and began to make the sacrifices that might preserve this American way of life. Voluntarily, we have accepted military conscription; voluntarily, we are giving up our business, our professional lives and our family ties to further the great business of national defense; voluntarily, we have assumed increased taxation, burdensome debts and obedience to dictatorial powers, that, in the end, we might return to our free way of living.

We have, however, no guarantee that our liberties will be returned to us unless we ourselves retain a spirit of freedom that will require their return. Planned economies are still in the making, and it is said that federal socialization of medicine has by no means been permanently abandoned.

It will be well for us all to remember the words of Benjamin Franklin: "You have a Republic, if you can keep it."

## SANATORIUM CARE FOR RHEUMATIC CHILDREN

LAST May, the Sharon Sanatorium closed its doors to patients with tuberculosis. In the fall of 1938, a small group of children with rheumatic fever were placed in an isolated pavilion; this step was owing to the fact, now increasingly apparent, that the ultimate prognosis in this disease is determined not so much by the onset as by the insult of repeated attacks, which are so often precipitated by infections of the upper respiratory tract. The children were protected, so far as possible, from exposure to infections of the upper respiratory tract, lived on open porches, even during the winter, and were kept on more or less of a tuberculosis regime. The preliminary results of this study,\* undertaken jointly by the sanatorium and the Children's Mission to Children, were so satisfactory that the directors of the sanatorium became convinced that all the energies of the institution should be devoted to the care of rheumatic children.

In line with this change of policy, the sanatorium has been extensively rebuilt, and equipment for intensive clinical and laboratory studies has been installed. With a bed capacity of forty, divided equally between two buildings, the feature of small units has been preserved.

To provide for the sanatorium care and study of children with rheumatic infection is a new undertaking that should be followed with extreme interest by all members of the medical profession. If the results are confirmatory of those obtained with the preliminary group, it seems likely that a means will be provided for reducing not only the mortality but also the cardiac crippling that is the usual accompaniment of the disease.

\*Hubbard J. P. and Griffin W. A. Open air sanatorium care for patients with rheumatic fever and rheumatic heart disease. *New Eng J Med* 223:963-972, 1940.

## OBITUARY

### HENRY AUSTIN WOOD

1855-1942

On February 21, 1942, the long life of Henry Austin Wood, of Waltham, was closed at the age of eighty six. Born in Upton, Massachusetts, he

attended Exeter and Harvard, receiving his medical degree in 1883 and settling in Waltham in 1888. Here he practiced medicine and surgery through the professionally eventful years that followed, becoming one of those remarkable doctors whose friends are legion and whose accomplishments are almost legendary in their native heaths. Of the more than 4000 babies he delivered, probably over half were born in their homes. How many major abdominal operations he performed can hardly be estimated, but many recall protracted periods when they averaged one a day; if a day passed without one major operation, there were usually two or three of them on the day following. This volume of work may be easily surpassed in the activities of many specialists, but it must be recalled that the doctor personally attended to all the practice that generated these deliveries and operations, if one is to appreciate the immensity of Dr. Wood's daily, monthly and yearly rounds. For a quarter of a century, he served on the School Committee; for half a century on the staff of the Waltham Hospital; for many years on many local boards and committees of the city in which he worked and lived and of which he was a part. The remarkable thing, and in his later years the notorious thing, about Henry Wood was his capacity to endure this continual pressure. Younger doctors have frequently embarked on such a life, only to find themselves burned out at the end of a decade. Dr. Wood wore out scores of horses, and later when the Fords came, he wore out the Fords.

The qualities that permit a man to accomplish this are of interest. There must first be mental and physical vigor, but that is not all. Many a vigorous character has made a fair bid for similar accomplishment only to learn what every woman knows: that his wife must contribute quite as much to such a life as he himself. And other men are tripped in their headlong course by their children, or by their inability to secure the faithful ancillary services needed to keep such a practice rolling. Henry Wood was fortunate in all these ways, he attracted faithful servants, like Mary Manning and Frank Christmas; his children never tripped him up; but above all he married a discerning and unselfish person who over the years became equally well known and beloved in her adopted city—Anna Wharton Smith. She, two daughters and two sons survive him. Although it was not the sort of thing he talked about, in his declining years it was a great comfort that the younger son was carrying on his practice in the modern way.

D O'H

## MEDICAL EPONYM

## MURPHY MANEUVER

On December 18, 1902, Dr. John Benjamin Murphy (1857-1916) described the following diagnostic maneuver, to which his name is frequently given, before the New York Academy of Medicine. His paper appeared in *Medical News* (82:825-833, 1903), under the title, "The Diagnosis of Gall-Stones."

... The most characteristic and constant sign of gall-bladder hypersensitiveness is the inability of the patient to take a full, deep inspiration, when the physician's fingers are hooked up deep beneath the right costal arch below the hepatic margin. The diaphragm forces the liver down until the sensitive gall-bladder reaches the examining fingers, when the inspiration suddenly ceases as though it had been shut off. I have never found this sign absent in a calculous or infectious case of gall-bladder, or duct disease.

R. W. B.

## MASSACHUSETTS MEDICAL SOCIETY

## COMMITTEE ON MATERNAL WELFARE\*

CASE HISTORY: POST-PARTUM HEMORRHAGE  
FOLLOWED BY SEPSIS AND DEATH

A thirty-nine-year-old primipara was first seen when approximately two months pregnant and was followed for approximately every three weeks until the onset of labor. The prenatal care was excellent. The past history was not remarkable. The heart and lungs were normal, as was the blood pressure. The blood Wassermann reaction was negative. Measurements of the pelvis were said to be normal. Pregnancy was uncomplicated except for grippe at about seven months.

Labor was normal and lasted only six hours, being terminated by a simple forceps delivery. Previous to delivery, the patient had been given two injections of pituitary extract, each consisting of 5 minims. She sustained a first-degree tear of the perineum. There was difficulty in the delivery of the placenta, which was expelled only after the greatest effort. The central part of the placenta was described as pale and had apparently been firmly

attached to the uterus. There was no mention of unusual bleeding until two hours after the placenta had been delivered. At this time, the patient was said to have been flowing very freely. Ice, ergot, pituitary extract and morphine were administered. The patient suffered another severe hemorrhage the following morning, and she was given 500 cc. of citrated blood. On the fourth day, a septic temperature developed. Two more transfusions were administered. Death from sepsis resulted on the seventh day. No autopsy was performed.

*Comment.* The use of pituitary extract in such large doses cannot be condoned. Presumably, although the record does not state this, the administration was delayed until full dilatation. The intelligent use of pituitary extract in minim doses after full dilatation when there is no disproportion is good obstetrics and frequently results in normal delivery. The record makes no note of any difficulty in the delivery, nor did the patient suffer any severe lacerations. Episiotomy was not performed. Most obstetricians prefer episiotomy, with its resultant clean wound, to the ragged laceration that the perineum so often sustains. The description of the placenta leads one to think that some placental tissue may have remained because of a minor degree of adherent placenta, or possibly that a true area of placenta accreta existed. The hemorrhage following so long after delivery, with the description of the placenta, confirms this supposition, and the fact that no subsequent hemorrhage is recorded in no way contradicts it. There is no mention in the record that the uterus was invaded after delivery. A hemorrhage such as that described usually stimulates intrauterine investigation. If the uterus had been invaded and an accreta diagnosed, hysterectomy after transfusion would have been the logical course. If a piece of adherent placenta had been found as the cause of this post-partum hemorrhage, it might have been removed manually. At any rate, in the face of such hemorrhage, it would have been wise to have packed the uterus and, if hemorrhage continued, to consider the advisability of hysterectomy. According to the record, however, no subsequent hemorrhage developed, but sepsis did follow. It is quite possible, in spite of the lack of positive evidence, that the uterus in some way was invaded at the time of the severe hemorrhage. If this was so, the following sepsis may have had its beginning in this manipulation. This death occurred before the era of chemotherapy.

\*A series of selected case histories will be published weekly. Comments and questions by subscribers are solicited and will be answered by members of the committee. Letters should be addressed to the secretary, Dr. Raymond S. Titus, 230 Dartmouth Street, Boston.

## APPLICANTS FOR FELLOWSHIP

PUBLISHED IN ACCORDANCE WITH THE PROVISIONS OF THE  
FELLOWSHIP LAWS (CHAPTER V, SECTION 2) AS AMENDED MAY  
22 1941

## BARNSTABLE DISTRICT

- GRANDFIELD, ROBERT F., Pleasant Street, Sandwich  
Middlesex University School of Medicine, 1927 Sponsor  
Paul P. Henson, 149 Main Street, Hyannis
- RICE JACKSON M., 394 South Street, Hyannis  
Middlesex University School of Medicine, 1932 Sponsor  
Charles E. Harris, 568 Main Street, Hyannis

Donald E. Higgins, *Secretary*  
Main Street Cotuit

## PFAKSHIRE DISTRICT

- DOBELLE MARTIN, 253 South Street, Pittsfield  
University of Ghent, Faculty of Medicine, 1934 Sponsor  
John C. Roe, 16 South Street, Pittsfield
- ERRB HENRY H., Otis  
Middlesex University School of Medicine, 1935 Sponsor  
Fred H. Vohr, 28 Park Street, Lee
- HIRSCHMANN, KURT L., Lenox  
University of Munich, 1932 Sponsor H. Peter Mueller,  
Massachusetts General Hospital, Boston
- SCHILLER, LOUIS, 55 Bay State Road, Pittsfield  
Kansas City University of Physicians and Surgeons  
1932 Sponsor Edward R. Messer, Housatonic Street,  
Lenox

George S. Reynolds, *Secretary*  
7 North Street, Pittsfield

## BRISTOL NORTH DISTRICT

- GOGLIA, ALFRED A., 66 Broadway, Taunton  
College of Physicians and Surgeons, Boston 1936  
Sponsor Myer Bloom, 20 Cedar Street, Taunton
- William H. Swift, *Secretary*  
141 High Street, Taunton

## BRISTOL SOUTH DISTRICT

- BEER ERIC, 151 Main Street, Fairhaven  
University of Freiburg 1921 Sponsor Maurice Ken-  
ler, 300 Pleasant Street, New Bedford
- KINIEL, GEORGE, 41 North Main Street, Fall River  
University of Vienna 1921 Sponsor Samuel Sand-  
ler, 56 North Main Street, Fall River
- SILTO, JOSEPH A., 132 School Street, New Bedford  
Hahnemann Medical College and Hospital, 1940
- WARRBURTON, NORMAN W., 189 Bates Street, New Bedford  
Middlesex University School of Medicine, 1935 Sponsor  
Thomas B. Horan, 119 Mill Street, New Bedford
- Albert H. Sterns, *Secretary*  
31 Seventh Street, New Bedford

## ESSEX NORTH DISTRICT

- CHART STANLEY G., 84 Main Street, Andover  
Middlesex University School of Medicine, 1935 Sponsor  
Abraham Ash, Medical Arts Building, Haver-  
hill Street, Lawrence

- DISALVO, JOSEPH J., 191 Garden Street, Lawrence  
Middlesex University School of Medicine, 1936 Sponsor  
N. F. DeCesare, 57 Jackson Street, Lawrence
- GRANT, ARTHUR A., 118 Bailey Street, Lawrence  
University of Vienna, 1925 Sponsor Leonard B.  
Ainsworth, 351 Essex Street, Lawrence
- KAUFMANN, GUSTAV G., 15 School Street, Andover  
Rush Medical College, University of Chicago, 1938
- NELSON, CHARLES E., 288 High Street, Lawrence  
Middlesex University School of Medicine, 1936 Sponsor  
John G. Miller, 80 East Haverhill Street, Law-  
rence
- SABRAGH, JOSEPH N., 147 Bennington Street, Lawrence  
Boston University School of Medicine, 1939
- WHITE, SEYMOUR J., 24 Dewey Street, Lawrence  
University of Paris School of Medicine, 1935 Sponsor  
John T. Batal, 281 Haverhill Street, Lawrence

Harold R. Kurth, *Secretary*  
57 Jackson Street, Lawrence

## ESSEX SOUTH DISTRICT

- BENEDETTI, CHARLES C., Danvers State Hospital, Box 50,  
Hathorne  
Hahnemann Medical College and Hospital of Phila-  
delphia, 1940
- BERENSON, HILDA (ROSE) L., 249 Summer Street, Lynn  
Middlesex University School of Medicine, 1934 Sponsor  
Louis E. Barron, 79 North Common Street, Lynn
- BERENSON, WILLIAM, 249 Summer Street, Lynn  
Middlesex University School of Medicine, 1934 Sponsor  
Louis E. Barron, 79 North Common Street, Lynn
- BRANCH, DENTON R., 172 Washington Street, Apt. 25,  
Lynn  
New York University College of Medicine, 1940
- BRIERE, ARNOLD C., 34 Baker Street, Lynn  
Tufts College Medical School, 1940
- CHADWELL, VIRGINIA T., 26 Lexington Circle, Swampscott.  
Boston University School of Medicine, 1933
- MOHER, JAMES J., Hotel Edison, 1 Bank Square, Lynn  
Yale University School of Medicine, 1937
- MORTIA, GEORGE E., 58 Wallis Street, Peabody  
Middlesex University School of Medicine, 1933 Sponsor  
Philip J. Finnegan, 82 Washington Square, Salem
- MUSMAN, SAMUEL, 484 Western Avenue, Lynn  
Middlesex University School of Medicine, 1933 Sponsor  
Ellis Michelson, 81 North Common Street, Lynn
- NUSSBAUM, JULIUS, 291 Summer Street, Lynn  
University of Vienna, 1925 Sponsor Albert Conner,  
89 Broad Street, Lynn
- PALLOTIA, JOHN J., 76 Main Street, Essex  
Kansas City University of Physicians and Surgeons,  
1933 Sponsor T. Herbert Foote, 2 North Main  
Street, Ipswich
- POTASH, JACOB, 155 Broadway, Lynnfield  
Middlesex University School of Medicine, 1933 Sponsor  
Maurice O. Belson, 311 Commonwealth Avenue,  
Boston
- WEINER ABRAHAM A., 42 Essex Street, Saugus  
Middlesex University School of Medicine, 1934 Sponsor  
Harold M. Secen, 23 Nahant Avenue, Lynn
- J. Robert Shaughnessy, *Secretary*  
24½ Winter Street, Salem

## FRANKLIN DISTRICT

BOEH, LOUIS S., Conway.  
Middlesex University School of Medicine, 1933. Sponsor: Arthur W. Hayes, 78 Federal Street, Greenfield.

OLSON, JOHN H., Colrain.  
College of Physicians and Surgeons, Boston, 1936. Sponsor: Halbert G. Stetson, 39 Federal Street, Greenfield.

Harry L. Craft, *Secretary*  
Ashfield

## HAMPDEN DISTRICT

ALIFANO, JOHN J., 934 Main Street, Springfield.  
Middlesex University School of Medicine, 1933. Sponsor: Charles L. Furcolo, 14 Maple Street, Springfield.

BILSKI, THEODOR, 12 Pleasant Street, Westfield.  
University of Halle, 1922. Sponsor: Morris J. Ritchie, 80 Elm Street, Westfield.

BORENSTEIN, MORRIS V., 14 Maple Street, Springfield.  
University of Vienna, 1936. Sponsor: Joseph Hahn, 146 Chestnut Street, Springfield.

ERNST, ROBERT G., 64 Magnolia Terrace, Springfield.  
Yale University School of Medicine, 1939.

FRIED, MARCUS B., 532 Chestnut Street, Springfield.  
Kansas City University of Physicians and Surgeons, 1933. Sponsor: Harry R. Wheat, 20 Maple Street, Springfield.

IZENSTEIN, LOUIS A., 132 Belmont Avenue, Springfield.  
University of Cincinnati College of Medicine, 1938.

JORCZAK, JOHN S., 250 School Street, Chicopee.  
College of Physicians and Surgeons, Boston, 1930. Sponsor: Louis E. Hathaway, Jr., 4 Chestnut Street, Springfield.

KLAR, J. JOSEPH, 124 Ellsworth Avenue, Springfield.  
College of Physicians and Surgeons, Boston, 1935. Sponsor: Norman Popkin, 145 State Street, Springfield.

LEARY, JOHN E., 194 Summer Avenue, Springfield.  
Tufts College Medical School, 1940.

SCHWARTZ, LEO, 110 West Alvord Street, Springfield.  
Middlesex University School of Medicine, 1933. Sponsor: Edward Katz, 10 Chestnut Street, Springfield.

Wayne C. Barnes, *Secretary*  
146 Chestnut Street, Springfield

## HAMPSHIRE DISTRICT

FELSEN, HERMAN, 191 Main Street, Easthampton.  
Anderson College of Medicine, Glasgow, 1937. Sponsor: Lucius B. Pond, 115 Main Street, Easthampton.

MATHIAS, ERNST E. M., 310 Elm Street, Northampton.  
University of Koenigsberg, 1912. Sponsor: Edward J. Manwell, 16 Center Street, Northampton.

Joseph R. Hobbs, *Secretary*  
16 Center Street, Northampton

## MIDDLESEX EAST DISTRICT

ADAMS, RAYMOND D., 1 Wildwood Terrace, Winchester.  
Duke University School of Medicine, 1936.

BARONE, WILLIAM D., Stetson Hall, 2 Elmwood Avenue, Winchester.  
Middlesex University School of Medicine, 1936. Sponsor: George A. Marks, 330 Dartmouth Street, Boston.

PROCHNIK, JAMES J., 19 Yale Avenue, Wakefield.  
University of Vienna, 1919. Sponsor: Hyman Morison, 483 Beacon Street, Boston.

RUNCI, DOMINIC, 928 Main Street, Winchester.  
Middlesex University School of Medicine, 1936. Sponsor: Richard W. Sheehy, 21 Washington Street, Winchester.

Kenneth L. MacLachlan, *Secretary*  
1 Bellevue Avenue, Melrose

## MIDDLESEX NORTH DISTRICT

BROADY, HAROLD, 53 Loring Street, Lowell.  
St. Louis University School of Medicine, 1941.

BRUNELLE, PIERRE V., 300 Beacon Street, Lowell.  
Middlesex University School of Medicine, 1935. Sponsor: Leopold F. King, 308 Merrimack Street, Lowell.

CROCKER, OSCAR, Park Street, Pepperell.  
Middlesex University School of Medicine, 1933. Sponsor: Clifford L. Derick, 412 Beacon Street, Boston.

KARBOWNICZAK, JOHN J., JR., 465 High Street, Lowell.  
Middlesex University School of Medicine, 1936. Sponsor: Henry S. Glidden, State Infirmary, Tewksbury.

LEACH, HARRIET P., 23 Lowell Road, Chelmsford.  
Yale University School of Medicine, 1935.

TIGHE, THOMAS J. G., 480 Westford Street, Lowell.  
Harvard Medical School, 1940.

Raoul L. Drapeau, *Secretary*  
310 Merrimack Street, Lowell

## MIDDLESEX SOUTH DISTRICT

BIALOW, SOLOMON P., 55 Cloverdale Road, Newton Centre.  
Middlesex University School of Medicine, 1935. Sponsor: Hyman Shrier, 246 Pearl Street, Newton.

BLOOMENTHAL, ABRAHAM P., 5 Banks Street, Waltham.  
Middlesex University School of Medicine, 1934. Sponsor: Edward M. Hodgkins, 45 Bay State Road, Boston.

BURKE, JOHN E., 16 Ware Street, Cambridge.  
Tufts College Medical School, 1938.

CHASE, LOUIS S., 41 Hawthorn Street, Cambridge.  
University of Berlin, 1934. Sponsor: Boris E. Greenberg, 416 Marlboro Street, Boston.

DENNY-BROWN, DEREK E., 10 Coolidge Hill Road, Cambridge.

University of Otago Faculty of Medicine, Dunedin, New Zealand, 1924. Sponsor: Stanley Cobb, Massachusetts General Hospital, Boston.

EHRENTHEIL, OTTO F., 12 Priscilla Road, Brighton.  
University of Vienna, 1923. Sponsor: Hyman Morison, 483 Beacon Street, Boston.

EVANS, FRANCES E., 1277 Commonwealth Avenue, Boston (Allston).  
Tulane University of Louisiana School of Medicine, 1938.

HAWES, LLOYD E., 7 Newbury Street, West Somerville.  
Harvard Medical School, 1937.

HAY, WILLIAM E., 135 Washington Street, Brighton.  
University of Nebraska College of Medicine, 1930.

HILL, EDWIN V., 87 North Hancock Street, Lexington.  
Tufts College Medical School, 1939.

JAMESON, JAMES J., 489 Common Street, Belmont.  
Kansas City University of Physicians and Surgeons, 1932. Sponsor: Benjamin Spritz, 219 Belmont Street, Belmont.

- LOKER WILLIAM W, 85 Pleasant Street, Frammingham  
Middlesex University School of Medicine, 1935 Sponsor  
Thomas R Mansfield, 270 Commonwealth Avenue, Boston
- MACDONALD, MARTIN L., 67 Vernon Street, Waltham  
College of Physicians and Surgeons, Boston 1908  
Sponsor John J Curtin, 478 Main Street Waltham
- MESINA, SALVATORE J, 49 Pennsylvania Avenue, Somerville  
Boston University School of Medicine, 1937
- MULLIGAN FRANCIS J, 607 Washington Street, Newton  
Boston University School of Medicine, 1926
- NEWLANDER, HAROLD, 264 Ferry Street, Malden  
Middlesex University School of Medicine, 1933 Sponsor  
Burton C Grodberg 640 Main Street, Malden
- O'BRIEN DAVID F, 59 Boston Street, Somerville  
Boston University School of Medicine, 1940
- RISLER, ROSS W, 135 Washington Street, Brighton  
Indiana University School of Medicine, 1938
- ROBBINS, LAWRENCE L, 59 Frost Street, Cambridge  
University of Vermont College of Medicine, 1937
- ROWE, WINSTON J 27 West Central Street, Natick  
Tufts College Medical School, 1937
- SILVERSTEIN, LOUIS B, 756 Moody Street Waltham  
Boston University School of Medicine, 1927
- SMITH, HELEN O P, Middlesex County Sanatorium, Waltham  
Boston University School of Medicine, 1925
- STELLAR, LAWRENCE I, 58 Cloverdale Road, Newton Highlands  
Tufts College Medical School, 1938
- SCHLEICH, WOLFGANG, M F, McLean Hospital, Waverley  
University of Bonn, Germany, 1935 Sponsor Kenneth J Tillotson, McLean Hospital, Waverley
- SWEENEY, GUY R, 10 Turell Road, Medford  
Middlesex University School of Medicine, 1936 Sponsor  
Earle M Chapman, 266 Beacon Street, Boston
- TADDIO ARTHUR E, 44 Walnut Street, Natick  
Tufts College Medical School, 1938
- TULLOCH, PRESCOTT E, 371 Broadway, Somerville  
Middlesex University School of Medicine, 1929 Sponsor  
Barnett C Titelbaum, 176 Broadway, Somerville
- VAN HUYSEN, WILLIAM T, Boston Post Road, Weston  
Tufts College Medical School, 1939
- WIES DAVID, McLean Hospital, Waverley  
Tufts College Medical School, 1935
- Alexander A Levi, *Secretary*  
481 Beacon Street, Boston

## NORFOLK DISTRICT

- ANDOSCA JOHN B, 249 River Street, Mattapan  
Royal College of Physicians and Surgeons, London,  
1934 Sponsor John A Foley, 464 Commonwealth Avenue, Boston
- ASHLEY, ALTA, Children's Convalescent Home Wellesley Hills  
Vanderbilt University School of Medicine, 1937
- AUSTIN, GEORGE, JR., 21 Hawthorn Road, Brookline  
Harvard Medical School, 1934
- BAILEY, CHARLES C, 14 Autumn Street, Boston (Roxbury)  
University of Virginia Department of Medicine, 1937

- BROWNLEE ROBERT E, 266 Brookline Avenue, Boston, (Roxbury)  
Harvard Medical School, 1937
- DANIELS, JAMES T, JR, 197 Longwood Avenue, Brookline  
Georgetown University School of Medicine, 1936
- FIRCLSON, ALBERT B, 1818 Washington Street, Canton  
Cornell University Medical College, 1917
- FINE FLSTEIN, SAMUEL M 72 Edson Street, Dorchester  
Middlesex University School of Medicine, 1931 Sponsor  
Bernard A Godvin, 483 Beacon Street, Boston
- FORSTER, FRANCIS M, 50 Pine Plain Road, Wellesley  
University of Cincinnati College of Medicine, 1936
- GOULD, MALVIN, 71 Halifax Street, Jamaica Plain  
Middlesex University School of Medicine 1934 Sponsor  
Joseph Laseron, 37 Monroe Street, Roxbury
- KATZ KERMIT H, 122 Tilbot Avenue, Dorchester  
Boston University School of Medicine, 1939
- MYERS, MARVIN T 406 Centre Street, Jamaica Plain  
Kansas City University of Physicians and Surgeons,  
1931 Sponsor Robert Slater, 587 Beacon Street, Boston
- MIHALONIS JOSEPH P, 119 King Street, Dorchester  
Tufts College Medical School, 1937
- MILLER, LOIS C, 456 Parker Street, Roxbury  
University of Pittsburgh School of Medicine, 1937
- MILONE, ANTONIO P, 4354 Washington Street, Roslindale  
Middlesex University School of Medicine, 1934 Sponsor  
Charles J E Kichham, 12 Bay State Road, Boston
- OHRENBEEGER, HENRY W, 132 Stoughton Street, Dorchester  
Tufts College Medical School, 1939
- RATTIGAN, JOHN P, 15 Dell Avenue, Hyde Park  
Boston University School of Medicine, 1939
- SALTZMAN, CHARLES, Medfield State Hospital, Harding  
Boston University School of Medicine, 1935
- SANTACROSS, NICHOLAS L, JR, 627 Pleasant Street, Milton  
Harvard Medical School, 1940
- SIHERMAN, DAVID S, 226 Winchester Street Brookline  
Boston University School of Medicine, 1937
- SILVERMAN, SAMUEL, 591 Morton Street, Dorchester  
Harvard Medical School, 1938
- STEWART, CHARLOTTE A, Medfield State Hospital, Harding  
Yale University School of Medicine, 1938
- STONE, NATHANIEL M, 94 Naples Road Brookline  
Tufts College Medical School, 1937
- TEDESCHI, CESARE, BOY A, Harding  
University of Bologna 1928 Sponsor Arthur J  
Gavigan, Medfield State Hospital, Harding
- THANNHAUSER, SIEGFRIED J 93 Ivy Street, Brookline  
University of Munich, 1910 Sponsor Joseph H Pratt,  
30 Bennet Street, Boston
- TRACEY, MARTIN L 63 Longwood Avenue, Brookline  
Jefferson Medical College of Philadelphia 1936
- Timothy F P Lyons, *Secretary*  
270 Commonwealth Avenue, Boston

## NORFOLK SOUTH DISTRICT

- DAVIS, ALBERT, 191 Sea Street, Quincy  
Middlesex University School of Medicine, 1936 Sponsor  
Benjamin F Bornstein, 370 Commonwealth Avenue, Boston



HUSSEY, MAE G. S., 195 Upland Road, Quincy.  
University of Cincinnati College of Medicine, 1937.

JETTER, WALTER W., 6 Bay View Avenue, Hingham.  
University of Buffalo School of Medicine, 1931.

Henry H. A. Blyth, *Secretary*  
24 Russell Park, Quincy

#### PLYMOUTH DISTRICT

CHASE, JOHN S., 1004 North Main Street, Brockton.  
Harvard Medical School, 1937.

DOUGLASS, HECTOR B., 30 Bedford Street, Bridgewater.  
Middlesex University School of Medicine, 1936. Sponsor: Ralph C. McLeod, Goddard Hospital, Brockton.

FITZGERALD, EDWARD F., 430 Washington Street, Whitman.  
Georgetown University School of Medicine, 1939.

GOLDFARB, SAMUEL, 19 West Central Avenue, Onset.  
College of Physicians and Surgeons, Boston, 1936. Sponsor: Raymond H. Baxter, 6 South Street, Marion.

RUNGE, PAUL M., 827 Main Street, Brockton.  
Boston University School of Medicine, 1937.

VALICENTI, PETER R., 393 Union Street, Rockland.  
Middlesex University School of Medicine, 1937. Sponsor: Peirce H. Leavitt, Goddard Hospital, Brockton.

Ralph C. McLeod, *Secretary*  
Goddard Hospital, Brockton

#### SUFFOLK DISTRICT

BLANCHARD, STANLEY W., 411 Marlboro Street, Boston.  
Tufts College Medical School, 1905.

BLOOMFIELD, STANLEY T., 745 Massachusetts Avenue, Boston.  
Boston University School of Medicine, 1937.

BURKE, JACOB B., 28 Warren Avenue, Chelsea.  
Tufts College Medical School, 1939.

DABROWSKI, JULIAN, 635 Dorchester Avenue, South Boston.  
College of Physicians and Surgeons, Boston, 1930. Sponsor: John J. Federkiewicz, 155 Savin Hill Avenue, Dorchester.

DENTER, LEWIS, 514 Park Drive, Boston.  
Harvard Medical School, 1936.

FLYNN, SIMON A., Boston City Hospital, Boston.  
McGill University Faculty of Medicine, 1938.

GATEMAN, MURRAY, 505 Massachusetts Avenue, Boston.  
Middlesex University School of Medicine, 1934. Sponsor: Max Ritvo, 485 Commonwealth Avenue, Boston.

HOPKINS, ELIZABETH A., 25 Park Drive, Boston.  
Tufts College Medical School, 1939.

KAPLAN, ISADORE, Soldiers' Home Hospital, Chelsea.  
Middlesex University School of Medicine, 1936. Sponsor: William H. Blanchard, Soldiers' Home Hospital, Chelsea.

KARP, ISADORE A., 153 Shurtleff Street, Chelsea.  
Middlesex University School of Medicine, 1936. Sponsor: Arthur Berk, 270 Commonwealth Avenue, Boston.

KELEMEN, GEORGE, 414 Beacon Street, Boston.  
University of Budapest Medical School, 1913. Sponsor: Philip E. Meltzer, 20 Charlesgate West, Boston.

KINNEY, THOMAS D., 39 East Springfield Street, Boston.  
Duke University School of Medicine, 1936.

PALMIERI, SALVATORE P., 20 Davis Street, Boston.  
Tufts College Medical School, 1941.

ROSMARIN, ERNEST, 366 Commonwealth Avenue, Boston.  
University of Vienna, 1906. Sponsor: Joseph Goodman, 375 Commonwealth Avenue, Boston.

SOUTTER, LAMAR, 13 West Cedar Street, Boston.  
Harvard Medical School, 1935.

YOVINO, EMANUEL M., 510 Broadway, South Boston.  
Tufts College Medical School, 1931.

Hollis L. Albright, *Secretary*  
412 Beacon Street, Boston

#### WORCESTER DISTRICT

ANGYAL, ANDRAS, Worcester State Hospital, Worcester.  
University of Turino, 1932. Sponsor: Bardwell H. Flower, Worcester State Hospital, Worcester.

BERGIN, JOSEPH D., 5 Quincy Street, Worcester.  
Boston University School of Medicine, 1940.

BUONO, CHARLES L., 98 Beverly Road, Worcester.  
Middlesex University School of Medicine, 1934. Sponsor: Joseph P. Mulhern, 390 Main Street, Worcester.

CARTIER, ROLAND R., Rutland State Sanatorium, Rutland.  
University of Montreal Faculty of Medicine, 1933.

DURFEE, MARION B., Worcester State Hospital, Worcester.  
University of Colorado School of Medicine, 1934.

FAIRBANKS, EDWARD J., 22 Nelson Street, Webster.  
Harvard Medical School, 1937.

GALUSZKA, BRONISLAUS A., South Street, Barre.  
Tufts College Medical School, 1939.

JACOB, LOUISE H., State Hospital, Westboro.  
University of Colorado School of Medicine, 1938.

KELLY, FRANCIS J., Hahnemann Hospital, Worcester.  
Hahnemann Medical College and Hospital of Philadelphia, 1941.

KRETZMER, EUGENE, 29 Maplewood Road, Worcester.  
University of Munich, 1908. Sponsor: George D. Kaneb, 28 Pleasant Street, Worcester.

LANKENNER, PETER A., 522 Grafton Street, Worcester.  
Middlesex University School of Medicine, 1932. Sponsor: Joseph P. Mulhern, 390 Main Street, Worcester.

MINSKY, JOSEPH W., 40 Central Street, West Boylston.  
Mid-West Medical College, 1934. Sponsor: Paul P. Montag, 200 Highland Street, Worcester.

MULLOWNEY, JAMES P., 71 Jaques Avenue, Worcester.  
Loyola University School of Medicine, 1938.

SACHS, BARNEY E., 989 Main Street, Leicester.  
College of Physicians and Surgeons, Boston, 1934. Sponsor: Bennet I. Fielding, 60 Franklin Street, Worcester.

SEIDENBERG, DANIEL, 12 Pleasant Street, Spencer.  
Kansas City University of Physicians and Surgeons, 1929. Sponsor: James C. Austin, 176 Main Street, Spencer.

TEED, ROY W., 24 Congress Street, Milford.  
Middlesex University School of Medicine, 1935. Sponsor: Joseph Ashkins, 36 Pine Street, Milford.

George C. Tully, *Secretary*  
34 Elm Street, Worcester

#### WORCESTER NORTH

MARNANE, JOSEPH P., 31 Nutting Street, Gardner.  
Tufts College Medical School, 1938.

SHAPIRO, MORRIS W., Gardner State Hospital, East  
Gardner

Tufts College Medical School, 1939

WIAST JOHN A., 101 Prichard Street Fitchburg  
College of Physicians and Surgeons, Boston, 1936  
Sponsor Aherne P. Lovell, 52 Hartwell Street,  
Fitchburg

Edward A. Adams Secretary  
40 Oliver Street, Fitchburg

## CONGRESS ON MEDICAL EDUCATION AND LICENSURE

The thirty eighth Annual Congress on Medical Education and Licensure held recently in Chicago proved so interesting that as delegate from the Massachusetts Medical Society, I am presenting certain impressions of the meeting while the various happenings are still fresh in my mind.

On Saturday afternoon, February 14, I attended a long meeting of the Association of American Medical Colleges. Here for more than five hours, the matter of the accelerated program of medical education was discussed. The upshot of the discussion led to several resolutions which were passed by that body. Among the most significant were the following:

Approval by the association of the accelerated program as an emergency measure.

Minimum standards for an approved course to include four terms of not less than thirty two weeks each, and no student to graduate sooner than thirty six months after his registration as a first year medical student.

Standards of eligibility to an approved school not to be lowered.

The council of the association was ordered to negotiate with the proper governmental agency for the establishment of a student loan or scholarship fund not to exceed \$3,500,000 a year, loans or scholarships from such a fund to be awarded on the recommendation of their deans to students needing financial assistance to carry out the accelerated program.

The association did not approve at the present time of asking federal grants to help in the financing of medical education, such aid as was to be sought was clearly in order to help needy students rather than the financial state of any medical school.

Internships were not to be regarded as acceptable when they were of less than twelve months' duration.

No school was to feel any sense of compulsion to attempt an accelerated program. Unless such a program could be carried out effectively by any school without lowering the quality of the medical education offered, it should not be initiated.

Before these resolutions were passed, Dr. Walter Biering, of Iowa reported that sixty three schools had already made plans to proceed on the accelerated program. He gave a careful analysis of individual state board rulings, which showed the difficulties that certain states will have in modifying their medical registration laws to be compatible with an accelerated program of medical education.

Major Sam F. Seeley, of Washington, D. C., outlined the plans of the Procurement and Assignment Service. A complete account of this has been printed in the February 21 issue of the *Journal of the American Medical Association*, so that I shall not attempt to describe it here. Major Seeley, however, emphasized that the Procurement and Assignment Service will do all in its power to protect hospitals, medical schools and communities from medical

deprivation. It is hoped that enough volunteers who are not essential doctors will be found to yield an adequate supply of medical officers for the needs of the armed forces. He described the methods to be pursued for grading essential doctors and for the deferment from active service of commissioned officers who at present are doing work essential to civilian needs. The success of the plan will hinge on the readiness of all physicians to supply data by filling out in detail the form that will soon be sent them and on their unselfishness in being ready to undertake any type of work assigned them.

Dr. Willard C. Rappleye of New York City, added significantly to the afternoon's discussion. He traced the development of the accelerated plan and pointed out that it had come into being largely because the Selective Service System realized the urgent need of physicians for military and civilian use and failed to see the necessity in times like these of the long vacation for medical students hitherto in vogue. On the other hand he reiterated that although the emergency must be met standards of medical education must not be lowered.

As a concluding item on the program Dr. Fred Zippfe of Chicago, called attention to the present shortage of microscopes for the use of medical students. He suggested that a survey of the supply of microscopes be made by each school and that microscope loan pools be established in different schools through their alumni associations. Alumni owning microscopes and not using them regularly could do a great service in lending their instruments to students, because new ones are almost unattainable. By such means an adequate number of microscopes, properly conditioned could be made available to students at relatively little expense. He also pointed out that a shortage of blood counting equipment and blood pressure machines may develop.

On Sunday, February 15, I attended the meeting of the Council on Medical Education and Hospitals of the American Medical Association. The council supported the attitude of the Association of Medical Colleges toward the accelerated program of medical education, emphasizing, too, that the decision of a medical school to initiate such a program was not compulsory and should be reached only after a comprehensive survey of its own ability to speed up its program of education without deterioration of the quality of its medical instruction.

On Sunday evening, I attended a joint meeting of the Council on Medical Education and Hospitals and the Advisory Board of Medical Specialties. This provoked interesting points of view. It seemed fair to presume that specialists would be of use to the armed forces and would continue to be of use to the civilian population. Therefore new specialists should be developed to meet these needs, and the idea of continuing training for properly equipped young physicians should not be abandoned. Various suggestions concerning how this might be best accomplished were debated.

The Annual Congress on Medical Education and Licensure was held during the following Monday and Tuesday, February 16 and 17. All the papers that I heard were interesting, although I was especially impressed with the one on Monday morning by Professor William B. Munro, of Pasadena, California. His title was, "The War, the Colleges and Federal Aid." His viewpoint seemed to be that we had already developed in the United States, through our plan of wide collegiate education, a good many college graduates who by no means were well educated. If governmental funds were to be made readily available to colleges, he feared that emphasis thereby might be laid on the quantity of students accepted rather

than on the quality of the education that they received, and this to him seemed unwise. He stated that scholarships with which to assist needy students, should federal aid become available for this purpose, were better than loan funds because they could more easily be awarded on the basis of scholastic aptitude and need rather than on need alone. He concluded by saying that, in his opinion, endowed universities should do all in their power to maintain their independence. Evidently, he feared that too much in the way of governmental subsidy of education might lead to restriction rather than to liberality in thought and study.

Monday afternoon was devoted to a discussion of war problems. Colonel George F. Lull spoke for the Army, Surgeon General Ross T. McIntire for the Navy, Surgeon General Parran for the Public Health Service, Colonel Leonard G. Rowntree for the Selective Service System, and Dr. Irvin Abell for the Committee on Medical Preparedness of the American Medical Association.

The need for doctors was emphasized again. The type of training that would develop most desirable officers for the Army and Navy was described. What the Selective Service System has already accomplished was brought out very graphically. And, finally, that all doctors will be useful to the country in some manner was made very plain.

Dr. Harold S. Diehl, of Minneapolis, concluded the session with an interesting paper on "The Role of Medical Schools in the War." It seemed clear to him that, of necessity, medical students must play an increasingly significant part in the country's history. Already certain features of military medicine have become of great importance to the country's needs, and he suggested that medical educators might well begin to point their teaching in the direction of giving medical students a better knowledge than heretofore of these new matters. He suggested, for example, that "first aid" should be taught to first-year medical students. The emergency care of wounds and minor sepsis deserves more systematic attention than this topic often receives in the normal peacetime curriculum. Psychiatry is rapidly becoming of noteworthy significance. Public health, tropical medicine, dermatology and venereal prophylaxis are general subjects that Army officers report as being inadequately covered in the undergraduate courses, as evidenced by lack of knowledge in these matters on the part of newly inducted officers. Finally, aviation medicine should be taught more emphatically, especially from the viewpoint of its physiologic aspects. Aviation medicine offers an important field of endeavor to competent young men with sufficient basic knowledge and training to enter it successfully.

On Monday evening, I attended the dinner of the Federation of State Medical Boards. This ended in a prolonged discussion of the accelerated program, entered into by state health officers from all over the country. The conflict of certain medical registration acts toward such a plan was again described. Finally, the federation expressed itself as being in sympathy with the move toward an accelerated program of medical education, regarding this, however, as a war emergency measure rather than as a permanent change in policy. It was stated that, when necessary, state laws on medical registration should be so modified as to make acceleration permissible during the period of emergency.

The program on Tuesday dealt less with matters pertaining to war medicine.

The Congress on the whole was the most significant one that I have attended. I came home feeling that the medical profession is playing a major part in national de-

fense, and is solving the many problems with which the country is now faced in a manner both creditable and intelligent.

REGINALD FITZ

### "THE INNER WORLD OF THE CHILD"\*

The child's inner world is full of color and feeling. It is simpler than the world we know and sometimes happier. The child has little information, but a great deal of curiosity. This curiosity is usually an expression of his need for learning. Sometimes, it can be an expression of the child's anxiety or his fears.

The child imitates and acquires. He learns by doing and imagining. He wants to love and be loved. He is only vaguely aware of what adults see in the world around them. He knows the difference between pain and pleasure, having and not having, coming and going away, death, to him, means little more than going away.

The child has many needs of which he may not be aware, and often he finds it hard to make his wishes clear. Thus, he must depend on the adults around him to understand and take care of his needs in a healthy way.

Next to himself, in the inner world of the child, the mother and father—or their substitutes—are most important. They are king and queen of the child's court, the mountains on both sides of his valley. In the simplicity of his inner world, the parents loom like giants or heroes toward whom he has affectionate and anxious feelings. Parents often forget this; some never know it.

Between the external situation of his life and his internal emotions, the child has to strike some sort of balance or make some sort of adjustment. But there is always a gap between what he wishes and what he gets from reality, and that gap, or deficit, is what fantasy fulfills. Whether it is made up in play, by story-telling, in little private dramas or in daydreaming, his fantasy life is always significant. It shows the direction in which the wishes go, as well as the failure of environment to provide what the child wants. The fantasies of a child are naturally fantastic. When they become real, they may be the accomplishments of the world. Fantasies and only fantasies explain the pyramids of Egypt, or an empire. Sometimes, the child's dream is more important to him than reality, or anything else in the world, and far more beautiful. It is natural for him to have daydreams. Don't laugh at him, or you may kill the goose that lays the golden egg. At some time or other in childhood, every girl is Cinderella or Snow White, and every boy is George Washington or the Dutch lad who held his finger in the hole in the dike.

The child does not understand the outer world as we understand it, but he understands it by what is called *intuition*, especially how it feels toward him; for example, it is said that children and dogs sense instantly how strangers feel toward them. Usually, children know without being told how those around them feel. Children are not so unaware of things as they may appear to be; as Wordsworth said, they are "not in entire forgetfulness, and not in utter nakedness."

If there is hostility or financial tension in a home, children sooner or later are aware of it. If there is pain or suffering or insecurity around them, they know about it. If there is conflict between parents, children sense it; they do not need to be told. They soon learn to adjust them-

\*A "Green Lights to Health" broadcast given through Station WAAB by Dr. Merrill Moore on Saturday, December 20, and sponsored by the Public Education Committee of the Massachusetts Medical Society and the Massachusetts Department of Public Health.

Let it or take advantage of it. On this account and the good of the child, if for no other reason parents would present a united front to their children, and when it is possible, should keep in fair agreement. Otherwise, the child quickly learns to play one off against the other, and from the point of view of discipline such a child sits down between two chairs." That is how he learns to feel conflict in himself, and how to be undisciplined and disorganized, for a child takes on a part of the personality of each parent.

If a parent is disturbed or hurt, this can be reflected in the child's conduct, play or schoolwork. One teacher who has what I call emotional intelligence said to me recently, "When a child we know to be bright begins to do poor work, we always look to see what is wrong at home. This point has been emphasized by Dr. Douglas A. Thom, Director of the Habit Clinic for Child Guidance in Boston. Dr. Arlie V. Bock, who has made similar observations in his study of normal college students at Harvard, believes that when students who have good minds fail to do good work, it is usually the reflection of some inner emotional problem or a disturbance at home."

The child is aware of his own body, which is very important to him. He begins early to understand what he is told about it. He remembers part of what he is told, and sometimes he can use that information with a kind of inborn intelligence.

Children recognize and appreciate the truth. They may ask either direct or indirect questions. It is essential for the parent to be aware of the possibilities of indirect questions, and to try to satisfy the child's curiosity, but the parent should not be overconscientious and answer questions that have not yet arisen in the child's mind. This confuses and overstimulates the child. A single question may need to be answered many times, since the child's growing understanding gradually takes in different phases of the answer.

Very close to the heart of a child is his awareness of his own sex. This should be treated with conscious respect. Adults can do a great deal to disturb the emotional development of some children, through misinformation or teasing. I know one person whose usual approach to a child (if it is a boy) is to say, "Oh! what a pretty little girl!" This always gets a rise out of the child, which the adult enjoys. But sometimes the child is mortified or enraged, and this may be only fuel to the flames of vanity in a person who likes to show off or be cruel.

It is normal for children to exhibit and, in childish ways, to be unkind. But as they grow up and learn other pleasures, normal people tend to give up childish behavior. Small boys are naturally rough and aggressive, but modern nursery schools are doing a great deal to show parents how to deal with these impulses in a constructive way. Well-run nursery schools have much to offer parents as well as children, and a tactful, intelligent kindergarten teacher can do much to help the child bridge the gap between home and primary school, and thus make happy adjustments to the demands of a group of children of his own size and age and general capacity.

Next to kindness, the child's greatest need is to be told the truth—to be given information he can use—again and again. This is how the child gains intellectual security. After the truth, the child needs fairness in all dealings with him. Fair treatment means more to the child than many people realize. Some of the most violent deeds in the world have been done as the result of a hurt or defeated sense of fair play. Children understand that. A woman told me once that Lincoln's Gettysburg address

always brought tears to her eyes when she heard it. I asked her why. She said, "Because it makes me feel he was so kind and so fair!"

To boil it down to a few words, then, What does a child need to make his inner world well organized? His efforts well directed, his expenditure of energy balanced and his whole personality free from conflict and unnecessary suffering? What can he acquire from the world around him, including his parents? Ideally, a good constitution and healthful living conditions, an opportunity to play and to learn to work. Practically, the child needs what the adult needs only more of it. There is no limit to the amount of affection a child can take, short of spoiling him. He needs to be praised, guided and reassured. Parents should try to instill self-reliance and not teach children to fear, as some silly people do. A child needs science, in its elements and art. Show a child a miner's sea-shell, a fossil, an insect or an animal. Notice the pleasure it gives him. Or show him a picture, a statue, a poem or a place, and tell him the story of it. He will enjoy that and learn from it. A child's attention is easy to gain but not so easy to hold for his span of attention is short. However, all the time you are speaking to a child his brain is recording what you say, and his spirit is being fed by it.

All the time you are with a child you are giving him facts, experiences, good or bad suggestion, and beautiful or ugly images. It is out of this material that he builds the inner world of his mind. In this inner world, his self (or ego) lives. It is a self that the world may later come to know happily or unhappily. It is this self that has to deal with his emotions and his conscience and with the outside world. For a child to grow and function best and cope with what he has to meet to grow up and go through life, he needs health, protection, security, affection, guidance and discipline, a chance to develop independence and real opportunities to be happy and useful.

## DEATH

GOODWIN—HAROLD C. GOODWIN, M.D., of Springfield, died March 1. He was in his sixty-fourth year.

Born in Peabody, Dr. Goodwin received his degree from Dartmouth Medical School in 1900. He was division examiner of prisoners for the Commonwealth of Massachusetts and was a member of the staffs of the Mercy and the Wesson Memorial hospitals and of the Mary Lane Hospital in Ware. He was a fellow of the Massachusetts Medical Society and the American Medical Association.

He is survived by his widow and two sons.

## MISCELLANY

### RESULTS OF THORACOPLASTY

The number of persons whose pulmonary tuberculosis has been arrested through the aid of thoracoplasty is steadily increasing. They will require medical surveillance for the rest of their lives. They are not immune to other diseases. Since any doctor may be called on for advice, it is desirable that all members of the profession be familiar with the changes in the thorax that are brought about by thoracoplasty. An abstract of a recent discussion (Overholt, R. N. Permanent collapse therapy in pulmonary tuberculosis. *JAMA* 117:1681-1697, 1941) follows.

In advanced tuberculous disease, tissue destruction and cavity formation have taken place, the elasticity of adja-

cent segments of the lungs is frequently decreased, and the volume of the healthy lung is so reduced that it is incapable of filling the unyielding thoracic space. How can healing take place under such conditions?

Pulmonary cavities must be closed and must remain closed. Fibrous tissue must not tear under the strain of ordinary thoracic movement, to ensure against reactivation or hemorrhage. The scar must be solid, but at the same time its contraction should not pull thoracic viscera out of position to the extent that cardiorespiratory function is impaired. Certain patients are fortunate enough to make these adjustments spontaneously, arrest the process, and enjoy moderate activity without reactivation. For a second group, the problem has been solved by an adequate pneumothorax (or other temporary measure), which is maintained indefinitely with safety. There is a third group to which thoracoplasty is not applicable; patients who have disease so extensive and so distributed as to make it technically impossible to bring it wholly under control by any single method or combination of methods must be excluded from this discussion.

A significant proportion of tuberculous patients do not fall into the foregoing categories. The health of patients in this fourth group can be restored with surgical help. They are those patients who suffer from advanced disease with irreparable pulmonary damage.

A discrepancy exists between the volume of healthy lung and the volume of the thorax. Temporary measures have failed or present no reasonable chance of being effective. They have an equivalent of two healthy pulmonary lobes, the two on one side or one on each side. Preferably, the disease is stable. The thoracic cage can be refashioned and the diseased lung released from its anchorages. The permanently altered position of the chest wall provides a permanent collapse.

Modern thoracoplasty accomplishes the following: fibrous tissue is released, permitting cavity closure; pulmonary tissue, which has been partially damaged but not totally destroyed and whose elasticity has been impaired by fibrosis, is relaxed; limitation of motion is imposed on the diseased lung; the collapse of the lung can be made highly selective, with conservation of healthy portions of the lungs; and disturbances due to distortion of the thoracic viscera, such as upward displacement of the lower lobe and lateral displacement of the heart and great vessels, are corrected.

All these readjustments are common accomplishments of a free pleura pneumothorax and thoracoplasty. In addition to these considerations, there are added benefits that are unique for thoracoplasty: thoracoplasty adjusts the thoracic volume so that it comes to equal the volume of the healthy lung—in other words, the functionless portion of the lung is placed under permanent control; the risk of tuberculous or mixed empyema developing in an artificially maintained air space is eliminated; and the risk of spontaneous pneumothorax on the side of treatment is greatly lessened.

The ultimate fate of patients treated by thoracoplasty cannot be determined until more time has elapsed. However, a preliminary study made of patients treated successfully by thoracoplasty and discharged with the consent of their medical advisers is most encouraging. Of 107 patients discharged five or more years, 101 are living, 3 died of tuberculosis and 3 died of other causes. Of 315 patients discharged under five years, 308 are living, 1 died of tuberculosis, and 6 died of other causes.

Although exactly comparable end results are impossible to find, it is fair to assume that the severity and extent of the process from which the groups under discussion suffered were more threatening than those of the aver-

age patient undergoing sanatorium treatment. Yet they seem to fare better, for a study of 6906 patients discharged alive from various sanatoriums in this country revealed that only 60 per cent of those discharged with consent were living after a period of five years.

In support of the belief that permanent collapse increases the chances for lasting results, the author quotes Roberts from the *Brompton Hospital Reports* (1936) as follows: "It is shown that the chance of surviving five years in B 3 cases [not defined in the article] treated without collapse was 23.7%; with pneumothorax, 55.3%; and with thoracoplasty, 66.6%. Thus, the expectation of living five years is approximately three times as great in cases submitted to thoracoplasty as in the average B 3 case."

A questionnaire sent to patients treated by thoracoplasty and discharged with consent brought 293 replies. The great majority considered themselves well and were glad they had had a thoracoplasty; 83 per cent were able to work; and 70 per cent declared they had no limitation of arm or shoulder motion. Many letters that accompanied the questionnaire replies stated that the scar and changes in contour of the chest constituted a small price to pay for restoration of health, and many stated that their only regret was that the operation had not been performed sooner.

Several refinements of thoracoplasty have been made since de Cernville performed the first thoracoplasty in 1885. These include lung palpation at operation, specific mobilization and the liberation of anchoring structures over areas of disease, preservation of periosteal elements and subtotal scapulectomy to minimize deformity in partial thoracoplasty.—Reprinted from *Tuberculosis Abstracts*, February, 1942.

## CORRESPONDENCE

### STUDY AND TREATMENT OF CONTAMINATED WOUNDS AND BURNS

*To the Editor:* The Surgical Service of the Massachusetts General Hospital has entered into a contract with the Office of Scientific Research and Development of the United States Government for the study of contaminated accidental wounds and burns and their treatment. The value of the study will be increased if a large number of compound fractures, severe lacerations and extensive burns can be obtained. Toward this end the hospital wishes to notify physicians that facilities will be made available for the transportation and admission of suitable cases on the recommendation of the attendant physician. Ambulance service and admission may be secured through the Admitting Office of the Hospital (CAPitol 4300).

N. W. FAXON, M.D., *Director*

Massachusetts General Hospital  
Boston

## BOOK REVIEW

*A Manual of Bandaging, Splinting and Strapping.* By Augustus Thorndike, Jr., M.D. Philadelphia: Lea and Febiger, 1941. 144 pages, with 117 engravings. \$1.50.

This is a very handy reference work for those who wish to apply a neat dressing or bandage of any kind. Most of the book is devoted to well-drawn illustrations, which require very little explaining. It should prove popular at this time to the hundreds of people who have suddenly developed an active interest in first aid.

(Notices on page x)

# The New England Journal of Medicine

Copyright, 1942, by the Massachusetts Medical Society

VOLUME 226

MARCH 12, 1942

NUMBER 11

## CURARE TREATMENT OF SPASTIC CHILDREN\*

### Preliminary Report

ERIC DENHOFF, M.D.,† AND CHARLES BRADLEY, M.D.‡

EAST PROVIDENCE, RHODE ISLAND

FOR centuries, curare has been known as a drug that paralyzes voluntary muscle. For many years, clinicians have recognized that spasticity in the form of persistent involuntary contraction of the voluntary muscles is often one of the most serious obstacles to effective treatment of children with cerebral palsy. Only recently has it been suggested that the paralytic effect of curare might be used to reduce this spasticity and thus expedite the rehabilitation of these patients. The present study was undertaken with the hope of increasing knowledge concerning the clinical safety and efficiency of curare as a therapeutic weapon against spasticity and to establish some standards and criteria for its use.

Curare is made up of a mixture of liquid extracts of several plants of the Strychnos group, whose most striking pharmacologic action is paralysis of skeletal muscle. It was first taken to Europe by Sir Walter Raleigh in the latter part of the sixteenth century after he had observed that the South American Indians were using it as an arrow poison. When thus used, it killed its victim by causing respiratory paralysis. The physiologic action of curare was not thoroughly investigated, however, until the middle of the nineteenth century, when Bernard<sup>1</sup> reported that its site of paralytic action on skeletal muscle was at the myoneuronal junction. The drug was subsequently employed at intervals in Europe in the clinical treatment of spasmodic disorders, such as tetanus and epilepsy. However, it could be obtained only from the South American Indians of the Amazon region. The supply was uncertain, the concentration was variable, and the stability of the drug unknown. For these reasons and since overdosage killed the patient by respiratory paralysis, the extensive clinical application of curare was imprac-

tical until recently. In 1938, for the first time, large amounts of the drug of known origin were brought back to the civilized world by Gill,<sup>2</sup> and since that time considerable progress has been made in preparing and reliably standardizing curare for clinical use.

In a recent review, Goodman and Gilman<sup>3</sup> summarize the composition and action of curare somewhat as follows. One obtains it by brewing the stems, roots, bark and leaves of several varieties of Strychnos and boiling down the extract to a thick resinous mass. This is soluble in water and in alcohol. The active principles are alkaloids whose chemical structure and chemical basis of action are still unknown. The pharmacologic effect of curare is that of an autonomic blocking agent. It acts mainly on skeletal muscle and to a lesser degree on autonomic ganglions, preventing the response of these cells to nerve impulses or injected acetylcholine. Curare apparently acts directly on the cells themselves at the myoneuronal junction. It does not impair the formation of acetylcholine but prevents that substance from eliciting its usual response. Curare does not inhibit the response of the muscle cells to other forms of stimuli, since curarized skeletal muscle still responds to direct electrical stimulation.

In curare poisoning, the curarized muscle first shows fatigue and weakness, later flaccidity and finally complete paralysis. The muscles of the digits, the eyes and the ears are first affected, then those of the limbs, trunk and neck, and finally, after adequate doses, the muscles of respiration. Death is due to respiratory paralysis. The action of curare is supposedly transient, and life may be preserved if artificial respiration is employed until the drug is destroyed or excreted. It is supposedly partly destroyed in the liver and partly excreted through the kidneys. The drug is entirely ineffectual when given by mouth, unless absorbed through a wound or extensive ulcera-

\*From the Emma Pendleton Bradley Home.

†Formerly, assistant resident physician, Emma Pendleton Bradley Home.

‡Superintendent, Emma Pendleton Bradley Home.

tion in the gastrointestinal tract. Theoretically, physostigmine and Prostigmine are pharmacologic antagonists to curare in their stimulatory phase of action on ganglions and skeletal muscle.

Interest was first aroused in the possible therapeutic value of curare in neurologic disorders, such as cerebral palsy, by Bremer's<sup>4</sup> report in 1929 that small doses, insufficient to paralyze the intact skeletal musculature completely or to embarrass respiration, selectively relaxed the muscle spasm in animals with decerebrate rigidity. Hartridge and West,<sup>5</sup> in 1931, reported that curare removed the violent spasms of tetany in doses that failed to paralyze the animal. This indicated that doses sufficiently small to be safe in human beings might be of benefit in relaxing muscles that are pathologically hypertonic. West<sup>6</sup> suggested the term "lissive" for this action, which relaxes but does not paralyze. Burman<sup>7</sup> noted that curare was beneficial in certain spastic and dystonic states in human beings and later reported a girl with spastic paraplegia as one in a series of patients suffering from neurologic disorders whose muscular rigidity was diminished following 20-mg. doses of curare.<sup>8</sup> Burman made the interesting observation that in some patients the beneficial effects of the drug lasted for three or four days following injection. Pusitz et al.<sup>9</sup> reported using curare on 7 children with cerebral palsy, but did not specify the size or frequency of dosage in all cases. They described "weakness and lassitude" lasting well into the day following an injection of 45 mg., and noted that doses definitely smaller than those sufficient to produce paralysis relaxed hypertonicity in spastic muscles. Bennett<sup>10</sup> reported the treatment of 12 patients suffering from severe spastic paralysis with curare in doses of 10 mg. per 20 pounds of body weight injected every second day over periods of months. Improvement in terms of transiently reduced spasticity during the period of injection was noted in several cases. There was no permanent relaxation as the result of treatment. Bennett suggested that the use of curare might facilitate muscle training and physiotherapy in such cases.

Apparently, not more than 20 cases of cerebral palsy treated with curare have been reported in the literature, and in few of them are specific dosage and response discussed in any detail.

#### MATERIALS AND METHODS

The present study is based on observations of the effects of curare administered in various doses by each of several routes at various intervals to 6 children with cerebral palsy. The patients ranged in age from seven to twelve years; they were all

of normal or superior intelligence, and spasticity was a prominent symptom in all. These children were resident patients at the Emma Pendleton Bradley Home during the four-month period covered by these observations. They had been under the supervision of an experienced physiotherapist and of graduate nurses of the permanent hospital staff for several months prior to this study. While the patients were receiving curare daily, detailed records of their activities and reactions were kept by this staff, and daily observations and examinations were made by one of us (E.D.). Throughout the period of study, except for the time spent in administering the drug and in carrying out specific tests, each child continued his usual daily activities of physiotherapy, academic schooling, occupational therapy and free play, individually and in the group.

*Specific medication.* The curare used in this study is known commercially as Intocostin.\* This is a physiologically standardized extract of curare secured from the Amazon forests. It is supplied in sterile ampules, 1 cc. of the yellow, watery solution containing the equivalent of 20 mg. of a standard curare.

*Route of administration.* In an attempt to ascertain the most favorable route of administration, doses were given to each of 2 children on different occasions by subcutaneous, intravenous and intramuscular injection. As discussed below, the intramuscular route proved the most satisfactory, and subsequent determinations of optimum dosage and intervals of administration were made on the basis of this method.

*Dosage.* The optimum dosage for each child was determined by systematic noting of the clinical response to gradually increasing amounts given intramuscularly on separate days. The first dose was 5 mg., and on subsequent days the individual dose was increased approximately 5 mg. each time until mild paralytic symptoms of overdosage appeared. A maintenance dose was then established slightly (4 to 8 mg.) below this level. The constancy of response of each child to his optimum and paralytic doses was striking, and suggested a gratifying stability of potency of the curare preparation.

Once an optimum dose for a child was determined, the therapeutic effect of repeating this dose at intervals of one, two, three and four days or even longer was noted.

*Control periods.* To eliminate any confusion resulting from the possible beneficial effects of curare injection through suggestion or other psychologic

\*Supplied through the courtesy of E. R. Squibb and Sons, New York City.

means, the response of each patient to intramuscular injection of sterile saline solution was noted. This injection was given under precisely the same conditions as those of curare administration.

After each child had been on his maintenance dose for some time, a period of several days to several weeks without medication was arranged, and the response noted.

*Tests of response to curare.* Apart from the general observations by hospital staff of each child's response to medication, a number of standard clinical and laboratory tests were employed in an effort to record objectively any evidence of improvement or untoward reactions.

Three standard motor-performance tests used in the psychologic laboratory were employed in evaluating the response to varying amounts of the drug. The pin board, peg ball and tracing board were used, as described by Garrett and Schneek.<sup>11</sup>

Electrocardiograms, observations of the pulse and respiratory rates, blood pressures, body temperatures, urinalyses and determination of renal function and various blood chemical levels were studied in all 6 children at various points during treatment. Electroencephalograms, taken immediately before and soon after an injection of curare, were performed on 1 patient.

*Curare combined with other drugs.* Observations were made of the effect of curare on each child's response to amphetamine (Benzedrine) sulfate as an extension of studies previously undertaken at the Bradley Home.<sup>12, 13</sup> Daily morning oral doses of 10 and 20 mg. of amphetamine sulfate\* were administered for several days during the time that each patient was receiving his maintenance dose of curare at optimum intervals, and changes in his reactions were noted.

## RESULTS

### Clinical Studies

*Dosage.* Following the injection of small and therapeutically ineffective doses of curare, the children within a few minutes complained of being dizzy and feeling "heavy." They often rubbed their eyes at this time, but these symptoms seldom lasted more than ten minutes. On clinical examination, the muscles of the hands appeared less spastic and more relaxed than usual for periods up to an entire day following these small doses. There was no other persistent or delayed response to these amounts, however.

Following what was later determined to be the optimum individual maintenance doses of curare, a more definite and persistent response was noted.

In about fifteen minutes, the children felt "sleepy" for a brief period. Shortly thereafter, they were noted to be somewhat unsteady, with masked facies and some drooping of the eyelids. Double vision was a frequent complaint at this point, but these symptoms disappeared in about half an hour. For approximately two days after the injection, the patients stated that they felt "light" and "happy." For approximately four days, the muscles of the feet and legs, fingers, hands, arms and trunk were relaxed. The reduction of spasticity was more marked in the lower than in the upper extremities. During this period of relaxation, speech was clearer and motor performance definitely smoother than usual. Any drooling that had formerly been present was diminished.

About fifteen minutes after the administration of large, paralytic doses of curare, the children became pale and mentally confused. This lasted between thirty and forty minutes, and was accompanied by definite drooping of the eyelids and relaxation of the neck muscles, which allowed the head to drop forward. There was excessive perspiration, and slow shallow respirations. The symptoms, which were alarming and suggested shock, disappeared without special treatment in about forty minutes, for the following twelve hours, however, the body musculature was definitely hypotonic, and the children were listless. Lethargy sufficient to interfere with any treatment program persisted for about twenty-four hours. Relaxation of spastic muscles, however, was noted for five or six days. During the latter part of this period, following recovery from a state of sluggish hypotonia, relaxation and motor performance during periods of muscle training were better than when the drug was not given.

The responses of patients to curare can be classified as immediate (those coming on within fifteen minutes to half an hour after injection) and delayed (those first appearing about a day after the drug is given). These effects, as noted on the 6 children under investigation, are presented in Table 1.

*Optimum route of injection.* The general response of all children to various doses of curare as just described varied somewhat, depending on the route of administration. When curare was given intravenously, muscular relaxation appeared almost immediately, however, paralytic symptoms, with evidence of respiratory embarrassment, also appeared often and immediately and to an alarming degree. For this reason, the intravenous route was abandoned, since extreme paralysis was hardly an aid to treatment.

\*Amphetamine (Benzedrine) sulfate was supplied through the courtesy of S. H. Kline and French Laboratories, Philadelphia.



Subcutaneous injection of the drug in doses found efficacious by other routes gave no consistent or desirable response. Consequently, this method was discontinued.

Intramuscular injection, usually into the buttocks, gave a good physiologic response, without

ing accentuation of response to the repeated injection of the same amounts of curare, although the difference between optimum maintenance and paralytic doses was not great. This suggests that individual patients respond in a constant manner to identical dosage, and that the preparation of curare

TABLE 1. Summary of Physiologic Responses to Curare in Various Doses.

SIZE OF DOSE	IMMEDIATE RESPONSE			DELAYED RESPONSE		
	SYMPTOMS	SIGNS	THERAPEUTIC EFFECT	SYMPTOMS	SIGNS	THERAPEUTIC EFFECT
Minimal (sub maintenance)	Dizziness and heaviness (transient)	"Sleepy" eyes for 10 minutes	Relaxed muscles of hands for 24 hours	None	None	None
Optimum (maintenance)	Sleepiness for 10 minutes	Unsteadiness, diplopia, lid lag and masked facies for 30 minutes	Relaxed muscles in fingers, hands, arms, trunk and lower extremities for 4 days	Feeling of lightness and happiness for 2 days	Diminished drooling for 4 days	Good muscular relaxation, efficient performance and clearer speech for 4 days
Maximal (paralytic)	Mental confusion for 40 minutes	Neck drop, pallor, excessive perspiration and diminished respiration for 30 minutes	Hypotonicity for 24 hours	Lethargy for 24 hours		Good relaxation and efficient performance for 5 or 6 days

the immediate, alarming symptoms of paralysis that had followed intravenous administration. The intramuscular route was therefore selected for therapeutic use, and the remaining conclusions are reported on this basis.

*Optimum dosage.* As shown in Table 2, the optimum maintenance dose varied considerably from one child to another. In general, the patient with the most extensive and intense spasticity not only tolerated but profited from the largest doses as de-

used is accurately standardized and remarkably stable.

To eliminate any confusion concerning the role of suggestion in producing the clinical results noted, the patients were at various points in the study given intramuscular injections of sterile saline solution, or no injections at all. In each case, complete absence of the curare response was noted.

*Optimum intervals between injections.* Once the optimum maintenance dose of curare was established for each child, the effect of repeating this dose at varying intervals was studied. The most satisfactory therapeutic results appeared when curare was administered at four-day intervals. Under this regime, there was some initial lethargy, which wore off promptly and allowed two or three days of relaxation without loss of energy. During this period, a training program could be efficiently carried out for each child. At intervals shorter than four days, the patients under treatment were more or less constantly drowsy, sluggish and irritable. Although alarming symptoms were not encountered, each child's response to physiotherapy and to the usual program of activities was far from at its best. When the interval between injections was longer than four days, complete spasticity returned, and hence the same obstacles to treatment appeared that were encountered before the drug was used. The length of time required for the return of these symptoms was governed somewhat by the size of the dose, and also by the degree and extent of the spasticity.

*Clinical data.* Repeatedly recorded observations showed that the drug had no immediate or delayed

TABLE 2. Optimum Maintenance Doses of Curare for Each of the Children.

CASE No.	AGE	WEIGHT	HEIGHT	PRIMARY SYMPTOMS	MAINTENANCE DOSE OF CURARE	
	yr.	kg.	cm.		mg.	mg./kg. body weight
1	7½	17.3	113.0	Spasticity, generalized, severe	56	3.3
2	12	30.0	134.5	Spasticity, generalized, severe	60	2.0
3	9	24.1	120.5	Spasticity, generalized, moderate	40	1.7
4	10½	35.5	127.0	Spasticity, lower extremities, severe	56	1.5
5	9	32.3	143.0	Spasticity, generalized, moderate	32	1.1
6	9	29.5	129.5	Spasticity, generalized, moderate	32	0.9

terminated on a body-weight basis. In the present group of patients, the optimum maintenance dose varied between 0.9 and 3.3 mg. per kilogram of body weight. These are larger maintenance doses than those used by others.

The constancy of response to individual maintenance doses in each child was striking. In no case was there diminished response or any alarm-

effects on pulse rate, respiratory rate, blood pressure or temperature.

### *Laboratory Studies*

*Psychologic tests.* Standard performance tests from the psychologic laboratory were used as aids in evaluating each child's response to varying amounts of curare. The pin board, peg ball and tracing boards were used, and the responses scored as described by Garrett and Schneck.<sup>11</sup> The results do not lend themselves to graphic portrayal in summary form in the present report, but in general, improvement in speed and accuracy of performance paralleled the clinical impression obtained otherwise.

*Other tests.* Various other laboratory tests, including blood counts, complete urinalyses, tests of renal function, blood chemical studies, electrocardiograms and electroencephalograms, showed no deviation from normal as a result of the use of curare.

### *Therapeutic Effect of Curare*

The results so far described have been specific responses to the administration of a particular drug. They fail utterly to depict the dramatic therapeutic response shown by the children in terms of improved relaxation during the muscle-training periods and during participation in their daily activities. On adequate maintenance dosage, clinical improvement was noted in every activity in which the child participated. During physiotherapy, the children enjoyed a fuller range of motion than previously; their co-ordination was smoother and more rhythmic. There was less resistance to passive exercise, and apparently increased muscle strength was noted in all children. The best clinical results appeared twenty-four hours after injection, when the initial lethargy and hypotonia had worn off. For the next three days motor performances were carried out with relaxation of antagonistic muscles and those not in use.

The subjective response to the treatment, as illustrated by the children's conversation, was interesting. Such remarks as "I feel light," "I'm happy" and "I feel easy" were frequently heard. As the effects of the drug wore off, the children spontaneously said that they were "feeling heavy again." It is significant that although as a group these patients are easily upset and ordinarily resistant to medical or surgical procedures, they were actually pleased to have a fairly large needle plunged into the muscles of the buttocks because of the favorable effects of the drug.

The experience of being able to carry out motor activities that were new and more extensive than those previously enjoyed was stimulating to

patients whose previous progress had been slow and discouraging. One boy (Case 6) had been anxious to spin a "jack," but had lacked sufficient control of his fingers to carry out this fairly skilled act. Under curare, he easily accomplished this, and was pleased and stimulated by the result. A nine-year-old girl who could walk only with difficulty had long wished to run up stairs. Under curare, she soon found that she was able to realize this ambition.

With muscles and limbs free to carry out constructive exercise, the children appeared to develop muscle strength and motor control. This persisted after the drug was stopped. One boy who had always held his arm tightly flexed across his chest was for the first time taught to hold it firmly on the arm of a chair while under the influence of curare. Four weeks after the drug had been discontinued, he still carried out this newly acquired act with assurance and confidence.

### *Combined Effect of Curare and Amphetamine*

Amphetamine sulfate in oral doses of 10 and 20 mg. daily was given to all the children during a period when they were regularly receiving maintenance amounts of curare. Four children (Cases 1, 2, 3 and 4) responded with increased output of energy and enthusiasm for daily activities, and resulting acceleration of motor performance. The response of these children to amphetamine simulated that noted in behavior problem children, and was in contrast to that reported by Nichols and Warson<sup>13</sup> on another group of spastic children who were not receiving curare, but who were studied under comparable conditions at the Bradley Home. However, 2 patients (Cases 5 and 6) responded to amphetamine, as those noted in the other series did, by becoming irritable and distractible, with corresponding decrease in efficiency of relaxation and motor performance.

### DISCUSSION

The treatment of children with cerebral palsy consists essentially of muscle training and the application of special educational procedures. These patients must be taught to do what other children acquire naturally in the way of motor co-ordination and efficient use of their bodies. The use of drugs that temporarily decrease pathologic neuromuscular activity and the employment of orthopedic operations or apparatus as mechanical aids to body function are always supplementary. Alone, they have no curative value, but their utilization may for the first time make it possible for a spastic child to profit from a training program. If curare is to have a place in the treatment of children with

cerebral palsy, it is a supplementary but nonetheless vitally important agent.

The present study confirms other recent but scattered reports that curare is now available for clinical use in well-standardized, potent and stable form. It can be safely administered to children with cerebral palsy in individually adjusted doses that are larger than those previously suggested in the literature. These large doses are effective in reducing muscle spasm over a period of several days, and require intramuscular injection but twice a week. Because curare relaxes the spasm of hypertonic muscles in doses insufficient to cause complete paralysis or respiratory embarrassment, treatment that is therapeutically efficient is not accompanied by the alarming symptoms of threatened collapse, which are a constant threat in truly paralytic doses of the drug. However, in the present state of knowledge, efficiency combined with safety is attainable only when the dosage for each child is determined by a noting of the patient's response to each of several gradually increasing doses, injected intramuscularly and starting at approximately 5 mg. Conservatism at present suggests that the adjustment of dosage as indicated in this study should be supervised by a physician thoroughly familiar with the behavior reactions of healthy as well as spastic children.

It is encouraging that, in these 6 cases, progress under physiotherapy was definitely accelerated by curare. When amphetamine was added, the accomplishments of 4 of these children were even further increased because of the additional "drive" that was imparted by the latter drug. This is an effect noted in physically intact children,<sup>12</sup> but it has not been noted in spastic children. Without curare, amphetamine presumably stimulates the same drive, but because of rigid, unmanageable limbs, the child is frustrated in his attempts to ac-

complish what he more ardently desires and as a result becomes irritable or sulky.

There was no evidence that any tolerance to curare was established through its continued use. The response of individual patients to specific doses in a uniform fashion was outstanding.

#### SUMMARY

A standardized, stable preparation of curare was injected intramuscularly in 6 children with cerebral palsy. The result was improved relaxation and reduction of spasticity in hypertonic muscles. By systematic adjustment of the dosage for each child, it was found that from 0.9 to 3.3 mg. of curare per kilogram of body weight resulted in relaxation lasting approximately four days. No toxic or dangerous effects were encountered under the regime employed, and response to muscle training and to the educational program was definitely accelerated.

#### REFERENCES

1. Bernard, C. Note sur la curarine et ses effets physiologiques. *Bull. gén. de thérap.* 69:23-25, 1865.
2. Gill, R. C. *White Waters and Black Magic*. 369 pp. New York: Henry Holt and Company, 1940.
3. Goodman, L., and Gilman, A. *The Pharmacological Basis of Therapeutics*. 1383 pp. New York: The Macmillan Company, 1941.
4. Bremer, F. The tonus and contracture of skeletal muscles. *Arch. Surg.* 18:1463-1490, 1929.
5. Hartridge, H., and West, R. Note on the action of curare in tetany. *Brain* 54:508, 1931.
6. West, R. The pharmacology and therapeutics of curare and its constituents. *Proc. Roy. Soc. Med.* 28:565-578, 1935.
7. Burman, M. S. Curare therapy for the release of muscle spasm and rigidity in spastic paralysis and dystonia musculorum deformans. *J. Bone & Joint Surg.* 20:754-756, 1938.
8. *Idem*. Therapeutic use of curare and erythroidine hydrochloride for spastic and dystonic states. *Arch. Neurol. & Psychiat.* 41:307-327, 1939.
9. Pusitz, M. E., Lattimore, J. L., Gold, A., and Ebendorf, H. Biological and biochemical studies of curare: preliminary report. *J. Kansas M. Soc.* 31:374-379, 1940.
10. Bennett, A. E. Personal communication.
11. Garrett, H. F., and Schneck, M. R. *Psychological Tests, Methods, and Results*. 235 pp. New York: Harper and Bros., 1933.
12. Bradley, C., and Bowen, M. Amphetamine (benzedrine) therapy of children's behavior disorders. *Am. J. Orthopsychiat.* 11:92-103, 1941.
13. Nichols, I. C., and Warson, S. R. Drug therapy in cases of infantile cerebral palsy and allied disorders, with special reference to hyoscine. *New Eng. J. Med.* 221:888-891, 1939.

## PARADOXICAL HEMATEMESIS\*

## Report of a Case

FRANK HINMAN, JR, M D †

BALTIMORE

IT is said that among every 100 patients who enter the hospital is one whose chief complaint is hematemesis.<sup>1,2</sup> About half these patients leave the hospital with a diagnosis hardly more exact than "hematemesis, source doubtful or unknown."

The reasons for this lack of exact localization of bleeding in patients who vomit blood warrant a brief review. Shaw<sup>3</sup> classifies the causes of hematemesis as follows: intrinsic gastroduodenal le-

hemorrhage from the stomach should be differentiated from esophageal bleeding or hemoptysis arising in the air passages and oropharynx. Blood from the latter structures may be swallowed and subsequently vomited. Localization rests on the objective examination of all possible sources of bleeding. Jackson et al.<sup>4</sup> wrote "Inferential methods of diagnosis are subject to a large percentage error. Objective examination of all accessible portions of the air and food passages should never be neg-

TABLE 1 Specificity of Diagnosis in 1139 Cases of Hematemesis\*

DIAGNOSIS	GUTMANN <sup>5</sup> (1932)		RIVERS <sup>6</sup> (1932)		SHAW <sup>3</sup> (1933)		HELLIER <sup>7</sup> (1934)		PETER BENT BRIGHAM HOSPITAL		PERCENTAGE OF ALL CASES
	NO. OF CASES	PER CENT AGE	NO. OF CASES	PER CENT AGE	NO. OF CASES	PER CENT AGE	NO. OF CASES	PER CENT AGE	NO. OF CASES	PER CENT AGE	
Proved											44
Peptic ulcer	19	19	491	73	14	50	96	37			
Varices with cirrhosis or splenic anemia or both			18	3			74	8			
Carcinoma of stomach or other lesions of gastrointestinal tract	5	5	110	17	3	11	5	2			
Doubtful											28
Ulcer history with negative x-ray study or operation	15	15	72	3	11	39	106	35	19	47	
None made											26
Alcoholic history and large liver, but no proved varices	6	6	15	2					7	18	
Inconclusive history and no positive findings	55	55	12	2			72	23	14	35	
Totals	100		668		28		303		40		

\*These figures are not directly comparable, some statistics are from a medical service (Peter Bent Brigham Hospital) and some from surgical services (Rivers and Gutmann); some patients were admitted immediately after hematemesis (Gutmann and Peter Bent Brigham Hospital) and some entered after longer intervals (Shaw and Hellier).

sions; splenohepatic disorders; blood diseases; swallowed blood from epistaxis or hemoptysis; and hyperpiesis. These are arranged in the order of their frequency, and Shaw excludes those of rare occurrence.

Of importance because potentially their condition can be diagnosed and consequently can be treated by specific methods are the patients who fall into the fourth category of Shaw's classification, namely, those who swallow blood and subsequently vomit it. These constitute the cases of what may be called "paradoxical hematemesis," since the blood does not come primarily from the stomach. Whether or not actual hematemesis has occurred is often difficult to determine, but true

lected." Information from the history may be pathognomonic and, when combined with confirmatory physical signs and roentgenographic examination, makes an exact diagnosis possible. As indicated below, however, this accuracy is not the rule.

Table 1 summarizes the diagnoses in 1139 cases of hematemesis abstracted from the reports in the literature of the last ten years and from the records of the Peter Bent Brigham Hospital since 1913. The latter include only those cases diagnosed specifically as hematemesis. All these cases have been grouped under three headings: "proved diagnosis," "doubtful diagnosis" and "no diagnosis made," more or less as the authors used the terms or as they appeared on the records. In 44 per cent of the 1139 patients, the diagnosis was proved by x-ray examination, esophagoscopy, operation or

\*From the Medical Clinic, Peter Bent Brigham Hospital.  
†Formerly clinical clerk, Peter Bent Brigham Hospital.

autopsy; this group needs no comment. Twenty-eight per cent of the patients were classified as "doubtful," and no diagnosis was made in another 28 per cent. In other words, for more than half the patients with hematemesis, no exact diagnosis was made.

The "doubtful" group is composed of patients with a history of ulcer but lacking x-ray or operative confirmation. Many of these patients were classified as having peptic ulcer because of the history of indigestion and because of the frequent incidence of this disease. The regimen for the treatment of ulcer is fairly nonspecific and generally supportive in the majority of cases, so that this lack of exactness is harmful only in the small group of patients who have advancing lesions higher in the food passages.

Among the 28 per cent of patients grouped under the heading "no diagnosis made" are those with a well-substantiated history of alcoholism and an enlarged liver, but without objective proof that esophageal varices were present. The cases in which the diagnosis of ruptured varix was made or suggested (the second group in Shaw's<sup>3</sup> classification) are divided about equally between the "proved" group in which x-ray examination or esophagoscopy was diagnostic, and that of "no diagnosis made," in which these examinations either were not made or yielded no definite findings. The latter group contains the overlooked lesions causing hematemesis, such lesions being esophageal ulcers, carcinomas, diverticulums, pulmonary lesions, vascular disorders and pharyngeal erosions. Ruptured esophageal varix is often a diagnosis of exclusion.

The rationality of Jackson's<sup>4</sup> advocacy of thorough objective examination of all possible sources of the bleeding is admirably illustrated by the following case.

CASE REPORT

M. J. G., a 60-year-old man, was admitted to the Peter Bent Brigham Hospital on June 15, 1939. He had long been in the habit of drinking at least 8 ounces of whiskey several days a week, but he had been well, had lost no weight, and had worked, as a mason's helper, until the onset of his illness. His appetite had been fair, and he had had no indigestion. Three days before entry, he had periumbilical cramps, which lasted 1 day. Twenty-four hours before admission, he vomited dark clotted blood. He repeated this at intervals until admission, losing in all about 250 cc. of blood. The blood was expelled without nausea or cough; it simply welled from his mouth. He was given morphine in the hospital, and the hematemesis ceased. Examination showed only questionable increase in the size of the liver and bilateral, solitary, firm cervical nodes. X-ray films of the chest and abdomen after a barium meal showed no changes from the normal. After an uneventful course in the hospital, the patient was dis-

charged with the probable diagnosis of cirrhosis of the liver and rupture of an esophageal varix.

One year after discharge, the patient reported to the Outdoor Department complaining that during the last 6 months the right cervical lymph node had increased in size. Examination and biopsy demonstrated squamous-cell carcinoma of the right tonsil. He was given 4000 r of roentgen therapy, with only temporary improvement; in fact, 1 month after the termination of therapy, a smooth, round mass was found at the base of the tongue.

The last (and diagnostically decisive) admission was on February 4, 1941. For 3 days, the patient had "brought up" bright-red blood intermittently, and the day before entering he had expelled about 500 cc. of dark blood mixed with gastric contents. That afternoon, he felt weak and passed several tarry stools. On admission, he had a thick tongue, with a firm, rounded mass on the right lateral margin extending backward to the base of the tongue and onto the lateral wall of the pharynx. The palatine fossa on the right was "punched out." Firm nodes were felt in the neck, bilaterally. X-ray examination showed no abnormality of the esophagus, stomach, duodenum or lungs but, with the patient swallowing barium, demonstrated what "appeared to be a large ulcerated area in the region of the right tonsil." At no time while the patient was in the hospital could actual bleeding from the pharynx be seen, but no further hematemesis occurred. All observers believed that the carcinoma of the tonsil, extending into the tongue, had ulcerated and bled, the blood being swallowed and later regurgitated.

Two comments are appropriate. In the first place, the difficulties in making the correct diagnosis are typical. An equivocal history from a patient who had an alcoholic past and a large liver, combined with hematemesis, seemed to make the diagnosis of bleeding from an esophageal varix obligatory, in spite of the lack of positive evidence by x-ray examination or esophagoscopy. Yet all that was needed to make the correct diagnosis on

TABLE 2. Incidence of Bleeding in Carcinoma of the Tonsil.

DATA	PETER BENT BRIGHAM HOSPITAL	COLLIS P. HUNTINGTON MEMORIAL HOSPITAL*	LITERATURE†
Total admissions	124,783	15,291	(Not known)
Cases of carcinoma of tonsil	7	100	1226
Cases with hemoptysis	2	2	4
Cases with hematemesis	1	0	0

\*Admissions limited to cases of cancer.  
†Pack and LeFevre<sup>9</sup> (1930), New<sup>10</sup> (1931), Coutard<sup>11</sup> (1932), Mattick<sup>12</sup> (1939), Schall<sup>13</sup> (1934), Duffy<sup>14</sup> (1934) and Richards<sup>15</sup> (1936).

the first admission was an objective search with all possibilities in mind.

Secondly, the occurrence of bleeding from carcinoma of the tonsil is very rare. Table 2 summarizes the cases at the Peter Bent Brigham Hospital (1913-1941) and the Collis P. Huntington Memorial Hospital (1930-1940) and from the litera-

ture Hemoptysis, caused by carcinoma of the tonsil, is unusual, and no report of hematemesis from this source was found in the literature during the last twenty-five years, although most authors make the statement that bleeding with subsequal hematemesis may occur from such pharyngeal sources. Speese and Skilern<sup>16</sup> report the case of an unconscious alcoholic patient who was brought in after vomiting a quart of dark blood mixed with gastric contents. At once, the diagnosis of cirrhosis of the liver with rupture of an esophageal varix was made. Later, however, careful examination showed that the patient had lacerated a coronary artery of the lip, that the blood had trickled down his throat while he was unconscious, and that he had vomited it.

Paradoxical hematemesis is recorded infrequently, but the diagnosis can be made more frequently if the possibility is kept in mind.

#### SUMMARY AND CONCLUSIONS

Hematemesis as a presenting symptom and a final diagnosis is reviewed by drawing on the records of the Peter Bent Brigham Hospital and on the experience recorded in the literature.

Emphasis is placed on the need for consideration of extragastric sources of bleeding. Although paradoxical hematemesis is relatively infrequent, the possibility should be borne in mind so that an

extragastric source will not be overlooked on routine examination.

A case of paradoxical hematemesis is reported in which ulceration in a carcinoma of the tonsil was the source of bleeding—an exceedingly rare occurrence.

Johns Hopkins Hospital

#### REFERENCES

- 1 Miller T G Gastric hemorrhage from internist's point of view analysis of one hundred and fifty-one cases *Pennsylvania M J* 32:237-241 1929
- 2 Hinton J W Discussion of Goldmann L Gross hemorrhage from peptic ulcer its morbidity mortality and treatment *J A M A* 107:1537-1547 1936
- 3 Shaw M E The causes and treatment of hematemesis *Clin J* 63:23-31 1934
- 4 Jackson C Tucker G Clerf L H Lukens R M and Moore W F Hematemesis a plea for objective methods of diagnosis *J A M A* 85:870-875 1925
- 5 Guimann R and Demole M J Sur l'origine des hematemeses *Full et mem Soc med d hop de Paris* 48:56-58 1937
- 6 Rivers A B and Wilbur D L The diagnostic significance of hematemesis *J A M A* 98:1139-1141 1932
- 7 Shaw M E Hematemesis *Lancet* 2:335-340 1933
- 8 Hellier F T Aetiology and mortality rate of haematemesis *Lancet* 2:1271-1274 1934
- 9 Pack G T and Lefevre R G The age and sex distribution and incidence of neoplastic diseases at the Memorial Hospital New York City *J Cancer Research* 14:167-294 1930
- 10 New G B Tumors of the tonsil and pharynx a report of 357 cases *Tr Am Laryng A* 53:277-309 1931
- 11 Coutard H Roentgen therapy of epitheliomas of the tonsillar region hypopharynx and larynx from 1920 to 1926 *Am J Roentgenol* 28:313-331 1932
- 12 Vainick W L Epithelioma of the tonsil study of one hundred and sixty-two cases *New York State J Med* 39:1417-1492 1939
- 13 Schill L A Carcinoma of the tonsil a statistical study of two hundred and thirty cases *New Eng J Med* 211:997-1000 1934
- 14 Duffy J J Carcinoma of tonsil clinical study of one hundred and seventy-six cases with histologic diagnosis *New York State J Med* 34:865-869 1934
- 15 Richards G E Radiological treatment of cancer: methods and results 1928-1933 malignant lesions of tonsil and its pillars *Canad M A J* 35:385-390 1936
- 16 Speese J and Skilern P G Jr Hematemesis due to concealed hemorrhage from coronary artery of lip *Int Clin Series* 27:4:169 193 1917

#### CLINICAL NOTE

##### CHEMOTHERAPY IN TYPHOID FEVER\*

EGON E. KATTWINKEL, MD †

WEST NEWTON, MASSACHUSETTS

THE remarkable progress of chemotherapy as a science and the advent of new chemotherapeutic agents raise interest regarding this new form of treatment in all bacterial diseases. The literature contains few reports of its value in the treatment of typhoid fever and the sterilization of carriers. The success of sulfaguanidine in the following case justifies its report.

Saphir and Howell<sup>1</sup> and Enright<sup>2</sup> report apparent cures of two typhoid carriers with soluble idio-phthalein, in one case after failure with sulfanilamide. Levi and Willen<sup>3</sup> report the cure of a

carrier with sulfaguanidine after failure with soluble idio-phthalein, cholecystectomy and appendectomy.

#### CASE REPORT

Mrs J. D., a 39 year old housewife, had always been well except for a peptic ulcer in 1930 and colitis with blood and mucus in May, 1940. The latter diagnosis was verified by x-ray study. Apparent cure resulted from the use of belladonna, diet and rest. The stools were negative for amebas.

On April 1, 1941, the patient had a "cold," which improved during the next week. On April 5, she had chills and began running a daily temperature between 102 and 103°F. There was frequency and dysuria. On April 14, rose spots developed, and the next day the blood culture was positive for *Escherichia typhosa*. The subsequent clinical and laboratory findings are shown in Figure 1.

Because of persistent colon bacilluria, the patient was given several courses of sulfathiazole and sulfanilamide, these failed to clear the stools of *E. typhosa*. It was believed that the spiking temperature during the 3rd and 6th weeks of illness was due either to an exacerbation of typhoid fever or to pyelitis. A slight macular rash

\*From the Newton Hospital Newton Massachusetts  
†Preceptor Tufts College Medical School visiting physician and cardiologist Newton Hospital

‡While in the hospital this patient was for a time under the care of Drs. L. S. Miller and A. R. Fried

appearing on the 28th day of illness was thought to be due to sulfathiazole therapy. An intravenous pyelogram on May 27 was negative for obstruction or renal damage, except for slight stasis in the right kidney.

On May 21, the patient suddenly developed a partial left hemiplegia following 2 days of numbness of the left

course of the disease and failed to clear the stools of *E. typhosa*. The stools became and remained negative after eight days of intensive sulfaguani-dine therapy.

65 Sterling Street

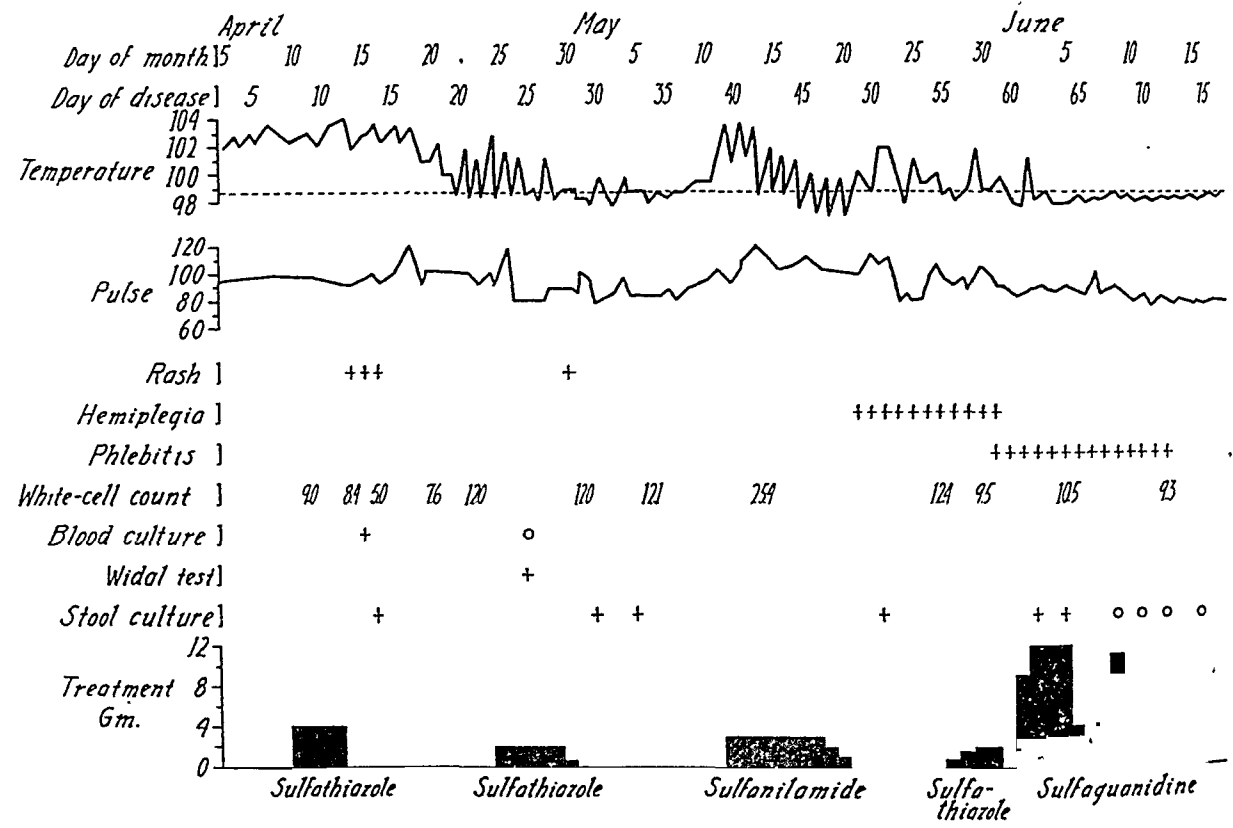


FIGURE 1.

arm. Lumbar puncture on May 23 was essentially negative. This episode was thought to be due to cerebral thrombosis, and the hemiplegia gradually disappeared in 2 weeks.

On May 31, the patient developed phlebitis of the left leg. Because of the lack of fever, this may have been a sterile thrombosis.

A Graham test showed a nonfunctioning gall bladder.

Because of persistently positive stool examinations for *E. typhosa*, the patient was given sulfaguanidine in large doses from June 2 to 16, and on June 9 the stools became negative and remained so. (Monthly stool cultures up to and including February 25, 1942, have been negative.)

When seen on July 12, the patient had gained 12 pounds and was symptom free except for slight weakness of the left cheek, slight swelling of the ankles at night and falling hair.

Up to the present time, investigation by the Massachusetts Department of Public Health has failed to reveal the source of this infection. The likeliest cause was food eaten 10 days before onset, while the patient was at a bridge party.

SUMMARY

A case of typhoid fever is reported. Sulfathiazole and sulfanilamide in no way influenced the

REFERENCES

1. Saphir, W., and Howell, K. M. Soluble iodophthalein in treatment of carriers of typhoid-paratyphoid group. *J. A. M. A.* 114:1988-1990, 1940.
2. Enright, J. R. Apparent cure of a typhoid carrier with soluble iodophthalein. *J. A. M. A.* 116:220, 1941.
3. Levi, J. E., and Willen, A. The typhoid carrier state treated with sulfaguanidine. *J. A. M. A.* 116:2258, 1941.

Erratum

In the article, "The Association of Primary Neoplasm of the Liver with Hemochromatosis," by Dr. Ernest W. Saward, which appeared in the February 12 issue of the *Journal*, several errors were inadvertently made by the editorial staff. The following corrections should be made:

Page 265, column 2, line 1. Change "(Fig. 1)" to read "(Figs. 1 and 2)."

Page 265, column 2, line 3. Delete "(Fig. 2)."

Page 265, Figures 3 and 4. Transpose the cuts appearing above the legends and change legend of Figure 3 to read, "Photograph of a Section of the Adrenal Gland."

## MASSACHUSETTS MEDICAL SOCIETY

## PROCEEDINGS OF THE COUNCIL

Stated Meeting, February 4, 1942

A STATED meeting of the council of the Massachusetts Medical Society was held in John Ware Hall, Boston Medical Library, 8 Fenway, Boston, on Wednesday, February 4, 1942. The meeting was called to order at 10:30 a.m. by the president, Dr. Frank R. Ober, Suffolk; 207 councilors were present (Appendix No. 1).

The Secretary presented the record of the meeting of the Council of October 1, 1941, as published in the *New England Journal of Medicine*, issue of November 6, 1941. On a motion by the Secretary and a second by a councilor, the Council approved the record as published.

*Report of Auditing Committee*

There was no response from the chairman, Dr. LeRoy A. Schall, Middlesex South.

*Report of Treasurer*

The report of the Treasurer (Appendix No. 2) was presented by Dr. Charles S. Butler, Suffolk. The report was accepted by the Council on the motion of Dr. Reginald Fitz, Suffolk.

The Secretary announced that his office is compiling a list of the fellows of the Massachusetts Medical Society who have entered the armed forces of the United States. He asked for the co-operation of the district secretaries in his endeavor to make this list complete. He added that at some future time the Council might wish to take particular notice of this patriotic service.

President Ober, at this point, called a meeting of the Committee on Public Relations. He asked the members of this committee to retire to the offices of the Society on the ground floor.

## REPORTS OF STANDING COMMITTEES

*Executive*

The Secretary presented the report of the Executive Committee (Appendix No. 3).

He spoke of a telegram which President Ober sent to the Governor of Massachusetts, the Honorable Leverett Saltonstall, on December 7, 1941, pledging the aid of the Massachusetts Medical Society in the crisis which had arisen that day. He read the Governor's answer. He announced that the Executive Committee had approved. He moved that the Council likewise approve this act

of the President. This motion was seconded by a councilor and carried.

The Secretary was directed on December 29, 1941, to send a telegram to the President of the United States embodying a resolution which had on that date been adopted by the Executive Committee. He read the telegram and President Roosevelt's answer. He moved that the Council likewise approve this act of the Executive Committee. This motion was seconded and carried.

He announced that the Executive Committee had reviewed certain matters which were to be presented by the Committee on Public Relations. He added that the Executive Committee commended the recommendations contained therein to the earnest consideration of the Council.

He reported on a special meeting of the Executive Committee which was held February 4, 1942, at 9:30 a.m. He read a resolution which was adopted by the Executive Committee. He added that the committee recommended its adoption by the Council and he so moved. The motion was seconded by Dr. Brainard F. Conley, Middlesex South.

Dr. Albert A. Hornor, Suffolk, in speaking for the adoption of the resolution said that he did not believe that we can hospitalize everybody who would be entitled to hospitalization under such a provision of taxation. He added that it was his belief that, if such a burden were thrown on hospitals at this time when we are anxious to be ready to take care of sudden War emergencies, hospital service would break down. He spoke of the present shortage of nurses and of the other difficulties to which the situation would give rise.

Dr. Channing Frothingham, Suffolk, inquired whether this matter had been considered before 9:30 that morning. President Ober answered, "No." Dr. Frothingham then said, "This is simply asking us to vote on a very important question without any consideration other than what the Executive Committee gave it at 9:30 this morning." He added that we really have not any definite program presented to us by the Social Security Department so that we may know what this is all about. He then asked if this was correct. President Ober by way of answer said that we have intimations of what the program is going to be. Dr. Frothingham then said that it is out of all



serious reason to introduce such a resolution now and ask us to vote on something that we know nothing about.

Dr. Conley in speaking in favor of the resolution called for confidence in the judgment of the Executive Committee and commended the committee for its alertness.

Dr. Charles C. Lund, Suffolk, expressed himself as being impressed by the seriousness of the subject under discussion. He asked that the Council be informed as to the background upon which this action of the Executive Committee was based. President Ober asked Dr. Michael A. Tighe to respond. Dr. Tighe said that the point which Dr. Lund made was well taken. It was expected by the Executive Committee that, in the debate which the presentation of the resolution would provoke, the background of knowledge which the Executive Committee possessed would be made available to the Council.

A few weeks ago there was a conference in Washington presided over by Mr. Altmeyer of the Social Security Department of the United States Government. Attending that conference were representatives of the American Hospital Association, Catholic Hospital Association and certain representatives of Blue Cross outfits from various parts of the country. Those attending that conference came away from it with the definite impression that it was the intention of the Social Security Department to call upon Congress for an extension of the present social-security coverage so as to include much greater numbers than it does now and so as to provide hospitalization for all so covered. The figures, as to those who would be covered in the extension, left the impression with the Executive Committee that this might well be the first step in the realization of the program presented some time ago in the report of the Interdepartmental Committee. We found much fault with this report when it was presented. You will remember that compulsory sickness insurance was an integral part of it. The Executive Committee was well aware that this matter had not reached the stage wherein a definite piece of legislation had been introduced into the Congress. Its purpose is to combat an idea which, if followed in its natural sequence, would be subversive of certain principles for which our organization stands.

Dr. John Homans, Suffolk, expressed the thought that it might be possible to add to the resolution a statement to the effect that the medical profession realizes the need of some form of prepaid medical care and is working to meet that need.

Dr. Leroy E. Parkins, Suffolk, asked that the resolution be read again.

President Ober at this point stated that the American and Catholic hospital associations, together with the Blue Cross associations and the American Medical Association, are cognizant of this matter and feel that we should do something about it before it starts.

The Secretary again read the resolution.

A demand for the question arose from several members of the Council. The question was put and the resolution adopted.

Dr. William M. Collins, Middlesex North, moved that the Committee on State and National Legislation, together with the officers of the Society, be instructed to follow closely the progress of this proposed legislation, using all the machinery at their command to oppose it. This motion was seconded by a councilor.

Dr. Lund offered the following amendment:

That the Committee on State and National Legislation and other officers of the Society be instructed to oppose such parts of the proposed legislation as seem harmful to the public and profession.

There was considerable discussion as to the advisability of publishing the resolution as proposed. Dr. Henry C. Marble, Suffolk, moved that it be not published in the minutes of this meeting but shall be written up. Considerable discussion followed participated in by Drs. Marble, Conley, Bearse, Chapman, Frothingham and Leavitt. Dr. Lund's amendment was recorded by a Councilor and carried on a show of hands. Dr. Collins's motion as amended was carried by vote of the Council.

### *Membership*

The report (Appendix No. 4), which was presented by the chairman, Dr. G. Colket Caner, Suffolk, recommended that twenty-three fellows be allowed to retire as of December 31, 1941, that seven be allowed to resign as of December 31, 1941, that the dues of ten fellows be remitted, that thirty-three be deprived of the privileges of fellowship, that ten fellows be allowed to change their membership from one district society to another without change of legal residence and that six fellows be recommended for readmission to fellowship.

Dr. Caner moved the adoption of the recommendations. The motion was seconded by a councilor. Dr. William E. Browne, Suffolk, expressed surprise that the committee's list contained the name of Dr. Seymour I. Zonn as one who had been dropped for nonpayment of dues. He asked Dr. Caner if this man had been notified of the fact that his dues were in arrears. Dr. Caner replied

that he had been so notified. Dr. Cancr's motion was adopted.

### *Financial Planning and Budget*

The report (Appendix No 5) was presented by the chairman, Dr. John Homans, Suffolk, who moved its adoption. The motion was seconded by a councilor.

Dr. Bearse inquired why the amount \$2000 set aside for medical defense was so large. Dr. Homans explained that this sum has been set aside against the possibility that it may be required this year.

Dr. Homans's motion was carried by vote of the Council.

### *Publications*

The report (Appendix No 6) was presented by the chairman, Dr. Richard M. Smith, Suffolk. This report announced that Dr. John F. Fulton, of New Haven, had been selected to give the Shit-tuck Lecture in 1942. It likewise spoke in praise of Dr. Robert N. Nye, managing editor of the *New England Journal of Medicine*. Dr. Smith moved the adoption of the report. The motion was seconded by a councilor and adopted by vote of the Council.

### *Arrangements*

This report (Appendix No 7) was presented by the chairman, Dr. William T. O'Halloran, Suffolk.

This report announced that the annual meeting of the Council will be held on the evening of May 25, 1942, and that the annual meeting of the Massachusetts Medical Society will be held on May 26 and 27, 1942. Both these meetings will be held at the Statler Hotel in Boston and promise to be larger than ever and to cost less.

### *Ethics and Discipline*

This report (Appendix No 8) was presented by the chairman, Dr. Ralph R. Stratton, Middlesex East. The report spoke of the three full-day meetings which the committee had held and said that the cases considered fell into four groups: first, those having to do with the ethical nature of proposed publications; secondly, those which were concerned with complaints against fellows for improper advertising; thirdly, those which grew out of alleged exorbitant charges by fellows; and, fourthly, those that charged violation of Article IV of the Code of Ethics of the Massachusetts Medical Society.

The report further spoke of the amicable way in which the matters referred to the committee had been settled.

Dr. Stratton moved the adoption of the report. The motion was seconded by a councilor and carried by vote of the Council.

President Ober at this point stressed the importance of the business before this meeting of the Council and urged all members to return to the meeting after luncheon.

### *Medical Education*

The report (Appendix No 9) was presented by the chairman, Dr. Robert T. Monroe, Norfolk.

This report spoke in praise of Dr. John P. Monks, who resigned as chairman, to enter the United States Navy.

It says that the membership of the Massachusetts Medical Society has grown during the last ten years from 4750 to 5676, an increase of nearly 20 per cent.

The number of applicants who have become fellows and who are graduates of approved schools has fallen off sharply in the last two years. From 1932 to 1939, they varied from 200 to 230 annually. In 1940, they fell to 179, and in 1941, to 115. During the same decade the number of graduates of unapproved domestic schools has remained essentially unchanged—22 to 38 in each year. The number of graduates of foreign medical schools rose from 4 or 5 through 1939 to 28 in 1940 and 60 in 1941.

The committee believes that admission to fellowship under the new by laws seems to be working out better than under the old and thinks it should be allowed to continue to exercise its discretion in the approval of candidates.

The committee is convinced that it would be a grave error to increase the time necessary for a reputable foreign physician to be resident in this country before being allowed to apply for fellowship in the Society.

The report concludes with the statement that the number of poorly educated graduates of unapproved domestic medical schools who enter the Society is too great.

It was moved and seconded that the report be accepted and so ordered by vote of the Council.

### *State and National Legislation*

The chairman, Dr. Henry C. Marble, Suffolk, no report.

### *Public Health and Public Education*

The report (Appendix No 10) was presented by the chairman, Dr. Francis P. Denny, Norfolk.

The report recommended that the weekly broadcasts known as "Green Lights to Health" be discontinued on the completion of the present pro-

gram, which will be about March 1, 1942. It says that the committee arrived at this conclusion because the morning hour assigned by broadcasting stations for these talks was much less satisfactory than the late afternoon time, which had formerly been given up to this matter, because the field of obstetrics had been ruled out entirely, because certain physiologic functions were no longer possible of reference and, finally, because the amount of good accomplished did not seem to justify the time which members of the Society would have to give in preparing the broadcasts—this latter in view of the numbers entering the service and the consequent increased demands on those who remained at home.

On motion by Dr. Denny and a second by a councilor the report was accepted and the recommendation adopted by vote of the Council.

### *Medical Defense*

Chairman, Dr. Arthur W. Allen, Suffolk, no report.

### *Permanent Home*

Chairman, Dr. William H. Robey, Suffolk, no response.

## REPORTS OF SPECIAL COMMITTEES

### *Cancer*

The report (Appendix No. 11) was presented by the chairman, Dr. Shields Warren, Suffolk.

The report spoke of the enthusiasm which was aroused generally by the publication of *The Cancer Manual for Practitioners*.

The committee feels that the Society should not be asked to support at this time the intensive campaign proposed for Massachusetts by the Women's Field Army. The committee believes that the compulsory reporting of cancer cases is not advisable.

The committee points to the excellent work being done by the state-aided cancer clinics throughout Massachusetts and says that these clinics are striking examples of how much benefit accrues to the public by this type of co-operation between the medical profession and public-health authorities.

Finally, the committee recommends that the president of the Massachusetts Medical Society be authorized to appoint a representative of the Society, preferably a member of the Committee on Cancer, to visit the various state-aided cancer clinics and report to the Society on their present state.

Dr. Warren moved the acceptance of the report and the adoption of the recommendation.

The motion was seconded by a councilor and so ordered by vote of the Council.

### *Public Relations*

This report was in two sections. Section A (Appendix No. 12A) was presented by the secretary, Dr. Elmer S. Bagnall, Essex North. It announced that the committee had given preliminary consideration to a postpayment plan for medical care sponsored by the banks and asked that the President be authorized to appoint a committee of three from among the members of the Massachusetts Medical Society to confer with the bank committee about this plan and that this committee report to the Council through the Committee on Public Relations.

Dr. Bagnall moved the adoption of this recommendation. The motion was seconded by a councilor and so ordered by vote of the Council.

Dr. Bagnall pointed out that each member of the Council had received material prepared by the committee on the subject of tax-supported medical care. He asked to be excused from reading it as a means of saving time. Dr. Bagnall moved that the recommendations contained in this part of the report be adopted. The motion was seconded and so ordered by vote of the Council. He also pointed out that in some localities cases in the insurance fields which involved hospitalization in wards had given rise to certain difficulties. The report recommended that the committee appointed to confer with the Massachusetts Hospital Association be instructed to meet with that body with a view to straightening out the difficulties involved. Dr. Bagnall moved the adoption of the recommendation. It was seconded by a councilor and so ordered by vote of the Council.

Section B (Appendix No. 12B) was presented by the chairman of the Special Committee on Prepayment Medical-Care Costs Insurance, Dr. James C. McCann, Worcester. This report contained nine recommendations which are concerned with the further development of the proposed Massachusetts Medical Service Corporation.

These recommendations are as follows:

1. That permission be granted the Massachusetts Medical Service Corporation to co-ordinate its activities with the Blue Cross relative to (1) the presentation of joint contracts to subscribers and (2) administrative functioning and expense. This shall be done with each group retaining (1) its distinct independent corporate identity and (2) the right to issue separate contracts, the relation of the two corporations to be determined on a contract basis.
2. That a special committee be appointed by the Executive Committee to select an executive director.

3. That authority be granted to the special committee to hire an actuary, provided that sufficient actuarial data are not made available to the committee through the Massachusetts Division of Insurance

4. That income levels for eligibility for medical service contracts (contrasted to medical indemnity contracts) be set up at \$2000 for an individual and \$2500 for a family. At present, only medical indemnity, and not medical service, contracts shall be offered above these levels

5. That contracts be prepared and presented on the following basis: (1) the quick preparation of a surgical contract for hospital surgical expense, (2) the preparation, as quickly as feasible, of a total hospital medical care contract to cover all medical fields incidental to hospital expense, (3) the careful slow preparation of a comprehensive medical-care contract covering total medical-care expense in the home, office and hospital, to be presented when the Massachusetts Medical Society so determines

6. That such sums as are indicated by the Commissioner of Insurance (presumably between \$10,000 and \$25,000) be loaned to the Massachusetts Medical Service Corporation by the Massachusetts Medical Society, and that other funds be raised by an enrollment fee from the participating physicians (to be returned to physicians enrolling within a given period of time, when as and if the corporation is financially able to do so)

[To complete action on this proposition and establish the Corporation, it is evident from the facts presented and from information received from the Commissioner of Insurance that but two subsequent steps are required: First, the preparation of contracts and, second, the preparation of a fee schedule]

7. That contracts be prepared

- (a) Between the physician and the Corporation,
- (b) Between the subscriber and the Corporation,
- (c) Between Blue Cross and the Corporation

8. That the contracts mentioned above and the statement to the Commissioner on the unit system be prepared and made effective by action at a combined meeting of the Committee on Public Relations and the Executive Committee

9. That a basic fee schedule be prepared, approved and put into effect for the Society by a group consisting of

- (a) The Committee on Public Relations
- (b) The Executive Committee
- (c) Appointees by the President in number and type to achieve an effectively balanced professional group, properly representing the general physician and the specialists in medicine

[The fee schedule is a basic proposition. (1) All are related to the New York Workmen's Compensation Schedule, which is accepted by physicians, government authorities and social workers as fair. (2) Various schedules are moderately lower in agricultural sections, and the same or moderately up in industrial sections. (3) It is anticipated that the Massachusetts schedule will be primarily based on the Michigan schedule, there must be a basic table accepted to be modified by experience after the Corporation begins to function. (4) There must also be presented to the Commissioner a statement of the method of compensation of the physician, which shall be on the unit system related to the accepted fee schedule.]

Dr McCann discussed each recommendation at considerable length and after offering, in each case, a most convincing argument, moved its adoption. In each instance his motion was seconded and so ordered by vote of the Council.

Recommendation No 5 was discussed by Dr. Channing Frothingham. He spoke as follows:

Unfortunately this plan so well prepared by Dr. McCann falls far short of the original ideas of the Council.

The records of the Council show that all the votes since April, 1939, on this subject make it clear that the Council has been interested in the development of a plan for the delivery of medical care on a prepayment basis. From the beginning this movement had the following objects in view:

1. To give more of the people of moderate means better medical care

2. To give better remuneration to physicians than they now receive for the medical care of people of moderate means

3. To permit more people to leave the charity clinics and return as private patients to physicians

4. To ally some of the agitation for governmental interference in the practice of medicine by satisfying more of the population

Although Dr. McCann's plan visualizes the possibility of comprehensive medical care at some future date, at present it simply offers some financial protection to those who are unfortunate enough to need surgery. Therefore, instead of offering medical care to the many, it only offers some financial protection to the few. This plan will not give better remuneration to the great mass of physicians as it only involves the surgeons. It will not make it possible for some of those patients who are now forced to go to the charity clinics for medical care to again become private patients of their own physicians. It will do very little more toward furthering the utilization of our ever increasingly effective preventive medicine. Further more it will benefit only a few of those people who are agitating for governmental interference in the practice of medicine and so accomplish little in averting this threat.

The question arises, Is it possible to develop a comprehensive medical care plan on a sound financial basis so that the original ideals of the Council can be fulfilled? From actual experience in several parts of the country it has been established that with from 10,000 to 20,000 subscribers a medical-care plan can be developed which will produce these results. The figures available from the White Cross experiment substantiate this. The White Cross operating on its adjusted pediatric and obstetric charges would with 20,000 subscribers pay its physicians adequately. There seems to be little doubt that subscribers to a scheme sponsored by the Massachusetts Medical Society would exceed these figures.

Another pertinent question is, Will the development of this plan before us make it more difficult eventually to develop a comprehensive medical care plan? There is some evidence to suggest that these plans for insurance to cover surgical fees lead to a marked increase in the amount of unnecessary surgery. In our state, in which so many poorly trained men are allowed to practice surgery, this possible increase in unnecessary surgery may be a real danger, especially if the Society insists upon free choice of physician rather than free choice of qualified physician. Therefore should this plan not succeed it might well give a black eye to the whole program of

furnishing comprehensive medical care on a prepayment basis.

This is the time at which the Council should decide whether it wants a comprehensive medical-service plan as it has always voted it did, or whether it wants a plan just to cover the financial emergency of unexpected surgery. If the Council prefers a medical-service plan, it should not vote to put into operation the plan as here presented, but should insist that the entering wedge should be the development of a plan for providing general medical care on a prepayment basis to certain groups. With the data already received by Dr. McCann and the experiences available regarding medical-service plans, it should be a relatively easy matter to develop such a plan in a short time.

In answer to a councilor Dr. McCann said that "one," "two" and "three" in Recommendation No. 5 outlined the sequence in which the Massachusetts Medical Service Corporation should offer contracts to the public. First, it should offer a surgical, obstetric and x-ray coverage only because this was at this time the safe way to approach the matter. When this part of the plan had been in operation for a while, sufficient experience would be gained so as to enable the Corporation to extend its coverage to the care of all types of hospitalized cases. The further experience thus gained he hoped would ultimately enable the Corporation to cover all types of sickness whether cared for in the hospital, home or office.

Dr. Norman A. Welch, Norfolk, spoke in favor of Recommendation No. 5 and emphasized Dr. McCann's statement that the type of coverage outlined in number one of Recommendation No. 5 was what the people really wanted at this time.

Dr. Homans asked for a discussion of Recommendation No. 6 before it was acted on by the Council. He wanted to know of the guarantee to the Massachusetts Medical Society that this sum of \$25,000 would be returned. He likewise wanted to know whether further sums would be asked for. Dr. Ober suggested that this money might be borrowed from a bank by the Massachusetts Medical Society at 4 per cent interest. He added that if the Massachusetts Medical Society put up the collateral the money could be had at a rate of 2½ per cent.

Dr. Charles J. Kickham, Norfolk, said that the Council voted to establish the Massachusetts Medical Service Corporation. The Insurance Commissioner requires a reserve of \$25,000 to be set up before such a Corporation can do business. He added that there was nothing else for us to do but to vote the loan. Dr. Homans suggested that the money might be obtained from some charitable fund. Dr. David L. Halbersleben, Norfolk, in objecting to this said that the Corporation should be in control of the Society itself.

Dr. Lund pointed out that \$25,000 means \$5.00 per member. He added that an assessment of \$5.00 per member would see this program through.

Dr. George L. Schadt, Hampden, asked if Dr. McCann had any information as to how this money might be raised. He answered that the Michigan State Medical Society had financed its own plan and that this phase of the subject had been discussed in the Committee on Public Relations. He added that the committee believed that as this was the Massachusetts Medical Society's program, its funds should be utilized for this purpose.

Dr. Edward P. Bagg, Hampden, spoke of how fruitful this meeting had been and moved that a special assessment of \$5.00 be levied on each member to make this movement possible. This motion was not seconded.

Dr. J. Harper Blaisdell, Middlesex East, directed certain questions to the Treasurer as to the net quick assets of the Society. Dr. Butler replied that the general fund of the Society is about \$132,000 and that this amount is largely in securities.

Dr. Blaisdell said that we have to come to a point where we either have to "put up or shut up." "We have to fish or cut bait." He added that this money should be voted from the free moneys lying in our account.

Dr. Homans wanted to know whether or not the \$25,000 spoken of was the limit of our obligation.

Dr. Butler said that, in the event that this money was loaned, it ought to be made clear that we would get it back again.

Dr. Conley said that this amounted to lending money to ourselves and added that it got to a point where we cannot trust ourselves with our own money.

At this point there were cries, "Question—question." The question was put and so ordered by vote of the Council, as previously recorded.

President Ober instructed the councilors that their district societies should create local professional-service committees in the near future. The by-laws of the corporation provide for a local administrative unit of nine persons—five physicians and four laymen. The former constitute the district professional-service committee; however, any additional number of physicians may be added to this committee, if it is deemed necessary. He added that such committees must be formed, by appointment or by election, in all districts before the corporation can begin to function.

#### *Postgraduate Instruction*

The report (Appendix No. 13) was presented by the chairman, Dr. Reginald Fitz, Suffolk. It

spoke of the wide interest shown in the New England Postgraduate Assembly which was held on October 29 and 30, 1941. The total attendance was 720 and seven states were represented. The receipts were \$301.41 more than the expenditures.

The postgraduate extension program for the present year has been organized in two divisions. One is financed by the Society for which a registration fee of \$5.00 will be charged and one, having to do with venereal disease, is sponsored by the State Department of Public Health; for this latter there will be no charge. Nine districts have signed up for the general course and three for that concerned with venereal disease. These courses are open to all legally registered physicians.

The committee has as yet arrived at no decision in the matter of a postgraduate assembly for next fall.

Dr. Fitz moved the adoption of the report. The motion was seconded and so ordered by vote of the Council.

#### *Physical Therapy*

There was no response from the chairman, Dr. Franklin P. Lowry, Middlesex South. (See Appendix No. 14.)

#### *Expert Testimony*

Chairman, Dr. George L. Schadt, Hampden, no report.

#### *Automobile Insurance Claims*

Chairman, Dr. Henry C. Marble, no report.

#### *Convalescent Care*

Chairman, Dr. T. Duckett Jones, Norfolk, no report.

#### *Industrial Health*

Chairman, Dr. W. Irving Clark, Worcester, no response.

#### *Army Medical Library and Museum*

Chairman, Dr. Henry R. Viets, Suffolk, no response.

#### *Study of the Practice of Medicine by Unregistered Persons*

Chairman, Dr. Richard Dutton, Middlesex East, no report.

#### *Committee to Meet with Massachusetts Hospital Association*

Chairman, Dr. Howard M. Clute, Suffolk, no report.

#### *Medical Preparedness*

The report (Appendix No. 15) was presented by the chairman, Dr. Reginald Fitz, Suffolk.

Dr. Fitz has nominated the following members of the Massachusetts Medical Society who will serve with him as a state committee to promote in Massachusetts the work of the Procurement and Assignment Service:

Dr. Howard M. Clute, Suffolk  
Dr. John J. Curley, Worcester North  
Dr. Edward L. Kickham, Norfolk  
Dr. Dwight O'Hara, Middlesex South  
Dr. Walter H. Pulsifer, Plymouth

These nominations will be subject to confirmation by Mr. McNutt, head of the Service at Washington.

On January 9, 1942, Dr. Fitz addressed each of the eighteen district presidents asking that a procurement and assignment committee be set up in his district. He reports that to date such committees have been organized in twelve districts.

On January 30, 1942, the names of forty-five physicians under the age of thirty-six, who had already enrolled with the Procurement and Assignment Service at Washington, were sent to Dr. Fitz "for scrutiny" as to the availability for "services elsewhere in the interest of the national emergency"—so as "to avoid the indiscriminate dislocation of practitioners who are in essential capacities." The names on this list have been submitted by Dr. Fitz to their respective districts and four of these districts have already reported. Dr. Fitz added that the results to date reflect credit on the Society.

He moved the acceptance of the report. The motion was seconded and so ordered by vote of the Council.

#### *Committee to Examine WPA Records*

Chairman, Dr. Guy L. Richardson, Essex North, no report.

#### *Maternal Welfare*

Chairman, Dr. Judson A. Smith, Suffolk, no response.

#### *Study of Practice of Medicine*

Chairman, Dr. Dwight O'Hara, Middlesex South, no report.

#### *Committee to Revise the By-Laws*

The chairman, Dr. Blaisdell, gave a verbal report in which he said that a rough draft of the by-laws was about ready. He said that when these by-laws are finally presented, many changes will be noted. He added that there will be an attempt to clarify the "five-year rule," that a new Standing Committee, to be known as the Hospital Relations Committee, will be recommended, that an attempt will be made to clarify the duties of the Secretary and Executive Secretary, that the du-

ties of the Executive Committee will be dealt with, that there will be a detailed consideration of the budget needs of this Council and finally that the status of assessments in district societies in relation to membership will be indicated.

He expressed the need for a special meeting of the Council, promising that the contemplated changes will be in the hands of the councilors two weeks before that meeting.

The Secretary pointed out that it also was the intention of the committee to call into conference all those committees which might be affected by the changes, preliminary to the presentation of the final draft to the Council.

Dr. Blaisdell moved that his report be accepted as a report of progress. The motion was seconded and so ordered by vote of the Council. Dr. Blaisdell moved that a special meeting of the Council be convened at such time as the President shall determine. The motion was seconded and so ordered by vote of the Council.

#### *Committee on Rehabilitation*

The report (Appendix No. 16) was ordered by the chairman, Dr. William E. Browne, Suffolk.

The report spoke of many conferences which the committee held with Professor Curtis Hilliard of the Massachusetts Committee on Public Safety and reiterated the Massachusetts Medical Society's time-honored stand of being privileged to be of assistance to those afflicted by disease or injury. Dr. Browne moved the adoption of the report. The motion was seconded and so ordered by vote of the Council.

Dr. Browne moved that the Committee on Rehabilitation be instructed to confer with Selective Service officials as to how the Massachusetts Medical Society might best co-operate in the matter of rehabilitation. The motion was seconded by a councilor and so ordered by vote of the Council.

Dr. Ralph M. Chambers, Bristol North, read a letter which was tabled.

#### APPOINTMENTS

President Ober offered the following appointments for action by the Council:

DELEGATES AND ALTERNATES TO THE HOUSE OF DELEGATES, AMERICAN MEDICAL ASSOCIATION FROM JUNE 1, 1942, TO JUNE 1, 1944:

<i>Delegates</i>	<i>Alternates</i>
David D. Scannell, Jamaica Plain	Elmer S. Bagnall, Groveland
Dwight O'Hara, Waltham	Ernest L. Hunt, Worcester
Charles E. Mongan, Somerville	Charles J. Kickham, Brookline
Walter G. Phippen, Salem	John I. B. Vail, Hyannis

DELEGATES TO THE ANNUAL MEETINGS OF THE MEDICAL SOCIETIES OF THE OTHER NEW ENGLAND STATES:

*Maine:* Warren H. Sherman, Lowell, and Carleton W. Bullard, Newburyport.

*New Hampshire:* C. Bertram Gay, Fitchburg, and John J. Curley, Leominster.

*Vermont:* George D. Henderson, Holyoke, and Wilfred A. Millet, Pittsfield.

*Rhode Island:* John A. Reese, Attleboro, and Howard P. Sawyer, Fall River.

*Connecticut:* Patrick E. Gear, Holyoke, and Wayne C. Barnes, Springfield.

DELEGATE TO THE ANNUAL CONGRESS OF THE AMERICAN MEDICAL ASSOCIATION ON MEDICAL EDUCATION AND LICENSURE AT THE PALMER HOUSE, CHICAGO, FEBRUARY 16 AND 17, 1942:

Reginald Fitz, Boston.

REPRESENTATIVES FROM THE MASSACHUSETTS MEDICAL SOCIETY TO A MEETING OF REPRESENTATIVES OF MEDICAL-SERVICE PLANS TO BE HELD IN CHICAGO, FEBRUARY 14, 1942:

James C. McCann, Worcester.

George L. Schadt, Springfield.

AD INTERIM APPOINTMENTS TO FILL VACANCIES:

Dr. Robert T. Monroe, Norfolk — chairman, Committee on Medical Education.

Dr. Chester S. Keefer, Suffolk — member, Committee on Medical Education.

Dr. James L. Chute — councilor, Barnstable.

Dr. Eliot Hubbard, Jr., — councilor, Middlesex South.

Dr. Louis F. Curran and Dr. Albert Ehrenfried — councilors, Norfolk.

Dr. William B. Castle — councilor, Suffolk.

COMMITTEE TO SELECT DIRECTOR OF THE MASSACHUSETTS MEDICAL SERVICE CORPORATION:

Peirce H. Leavitt, *Chairman*, Brockton.

Michael A. Tighe, Lowell.

Kenneth L. MacLachlan, Melrose.

William M. Collins, Lowell.

George L. Steele, Springfield.

DELEGATE AND ALTERNATE TO THE MEETING OF THE UNITED STATES PHARMACOPOEIAL CONVENTION AT CLEVELAND, OHIO, TUESDAY, APRIL 7, 1942:

Delegate: William B. Castle, Boston.

Alternate: James P. O'Hare, Boston.

REPRESENTATIVE FROM THE MASSACHUSETTS MEDICAL SOCIETY TO THE MENTAL HEALTH FOR DEFENSE ORGANIZATION, TO TAKE THE PLACE OF DR. A. WARREN STEARNS, RESIGNED:

Abraham Myerson, Brookline.

It was regularly moved and seconded that these appointments be confirmed, and it was so ordered by vote of the Council.

## NEW BUSINESS

Dr. Ober, in announcing the death of a councilor, spoke as follows:

Dr. Hugh J. Downey, a practicing physician and surgeon in Pittsfield for twenty-eight years, died on January 31 at the age of fifty-nine. Born in Adams, Dr. Downey received his degree from Loyola Medical College in 1912. Dr. Downey served as secretary of the Berkshire District Medical Society for ten years, or until 1939, when he was elected president of that district. He was an active member of the surgical staff of St. Luke's Hospital and was also a member of the House of Mercy staff. Dr. Downey was a delegate to President Hoover's Child Clinic Conference in Washington, D. C., representing Massachusetts, and to the Vermont Medical Council in 1938. He is survived by his widow, one son and one daughter.

At the request of the President, the Council stood in silence for one minute in tribute to the memory of Dr. Downey.

The President made the following announcement:

At the last meeting of the Council in October, 1941, the President and Secretary, on motion of Dr. Mongan, were directed to give their attention to the matter of the Approving Authority regulations, with a view of enlightening the Council as to the present situation. The President and Secretary have complied with this direction, and the information sought is contained in the *New England Journal of Medicine*, issue of November 13, 1941, pages 795 to 800.

The Secretary moved that the Council authorize the publication of a directory of the fellows of the Massachusetts Medical Society in 1942. The motion was seconded and so ordered by vote of the Council.

The Secretary announced that he was forced to bring to the attention of the Council an irregularity in which the censors of a district had certified a doctor in that district for membership in the Massachusetts Medical Society. This doctor had been so certified as the result of an examination which had been held on December 18, 1941. This examination should have been held on December 4, 1941. The Secretary suggested that the by-laws, as they relate to the time at which the censors' examination shall be held, be suspended in this particular case. Dr. Donald Munro, Suffolk, so moved. The motion was seconded and so ordered by vote of the Council.

Dr. Ober read a letter which he had received from Robert S. Harris of Massachusetts Institute of Technology. This letter spoke of a conference which would be conducted February 6, 1942, by the Massachusetts Committee on Public Safety on the matter of nutrition and asked that the Massachusetts Medical Society lend its name as a sponsor to this conference.

On motion of Dr. Shields Warren, Suffolk, and a second by a councilor, the Council voted to leave such matters in the hands of the President and Secretary.

Dr. Ober read a letter asking the Massachusetts Medical Society for a donation to a war fund which was being raised in Boston as a Boston activity. Dr. Ober pointed out that the Massachusetts Medical Society is a state-wide organization and, inasmuch as its members were aiding similar movements in their respective communities, he did not believe that the Society should contribute. No action was taken.

Dr. Munro addressed the Council to the effect that a doctor, who is not a member of a state or territorial medical society and who enters the Officer Corps of the United States Navy, may be commissioned an Ensign but cannot rise above that rank. He raised the question as to whether or not the Society's regulations governing admissions to membership might be waived or suspended for a period of time in the case of young doctors to whom sufficient time was not available to seek membership in the Society in the regular way.

He pointed out that the regulation which required examination of all prospective candidates by a board of censors was not merely a provision of the by-laws, but that such a requirement likewise appears in the articles under which the Massachusetts Medical Society was incorporated.

This subject provoked a great deal of discussion participated in by Dr. Munro, Dr. Homans, Dr. Halbersleben, Dr. Hornor, Dr. Mongan, Dr. Fitz, Dr. Blaisdell, Dr. Lund, Dr. Warren, Dr. Browne, Dr. Faxon and Dr. Conley.

Dr. Browne moved that the doctors described by Dr. Munro be admitted now, *de bene*, with the provision that they would later on satisfy the requirements of the Society. The motion was seconded and so ordered by vote of the Council.

Adjournment took place at 4:15 p. m.

MICHAEL A. TIGHE, *Secretary*

## APPENDIX NO. 1

ATTENDANCE — FEBRUARY 4, 1942  
COUNCIL MEETING

## BARNSTABLE

C. H. Keene  
W. D. Kinney

## BERKSHIRE

J. J. Boland  
R. J. Carpenter  
I. S. F. Dodd  
C. F. Kernan

## BRISTOL NORTH

W. H. Allen  
J. H. Brewster  
R. M. Chambers  
J. A. Reese

## BRISTOL SOUTH

F. M. Howes  
C. C. Tripp  
P. E. Truesdale



## ESSEX NORTH

E. S. Bagnall  
R. V. Baketel  
L. R. Chaput  
E. H. Ganley  
H. R. Kurth  
P. J. Look  
R. C. Norris  
G. L. Richardson  
A. F. Shea  
F. W. Snow  
C. F. Warren

## ESSEX SOUTH

Bernard Appel  
H. A. Boyle  
C. P. Brown  
C. L. Curtis  
Loring Grimes  
P. P. Johnson  
J. F. Jordan  
B. B. Mansfield  
A. E. Parkhurst  
W. G. Phippen  
E. D. Reynolds  
J. R. Shaughnessy  
J. W. Trask  
C. F. Twomey  
C. A. Worthen

## FRANKLIN

H. G. Stetson

## HAMPDEN

E. P. Bagg  
W. C. Barnes  
J. B. Bigelow  
W. A. R. Chapin  
G. B. Corcoran  
Frederic Hagler  
G. D. Henderson  
M. W. Pearson  
A. G. Rice  
G. L. Schadt  
G. L. Steele

## MIDDLESEX EAST

J. H. Blaisdell  
Richard Dutton  
E. M. Halligan  
J. H. Kerrigan  
K. L. Maclachlan  
G. R. Murphy  
R. W. Sheehy  
R. R. Stratton  
J. M. Wilcox

## MIDDLESEX NORTH

W. M. Collins  
R. L. Drapeau  
D. J. Ellison  
A. R. Gardner  
W. F. Ryan  
W. H. Sherman  
M. A. Tighe

## MIDDLESEX SOUTH

C. F. Atwood  
E. W. Barron  
W. B. Bartlett  
S. M. Biddle

## E. H. Bigelow

G. F. H. Bowers  
R. N. Brown  
R. W. Buck  
E. J. Butler  
B. F. Conley  
P. A. Consales  
H. F. Day  
C. L. Derick  
J. E. Dodd  
J. G. Downing  
C. W. Finnerty  
H. Q. Gallupe  
H. G. Giddings  
H. W. Godfrey  
Eliot Hubbard, Jr.  
A. M. Jackson  
A. A. Levi  
A. N. Makechnie  
Dudley Merrill  
C. E. Mongan  
J. P. Nelligan  
Dwight O'Hara  
Max Ritvo  
E. S. A. Robinson  
W. D. Roche  
M. J. Schlesinger  
E. F. Sewall  
E. W. Small  
H. W. Thayer  
J. E. Vance

## NORFOLK

Carl Bearse  
M. I. Berman  
G. F. Blood  
L. F. Curran  
William Dameshek  
F. P. Denny  
Albert Ehrenfried  
J. J. Elliott  
H. M. Emmons  
J. C. V. Fisher  
Susannah Friedman  
David Glunts  
B. T. Guild  
D. L. Halbersleben  
J. B. Hall  
R. J. Heffernan  
I. R. Jankelson  
C. J. Kickham  
C. J. E. Kickham  
E. L. Kickham  
D. L. Lionberger  
D. S. Luce  
C. M. Lydon  
D. L. Lynch  
T. F. P. Lyons  
Charles Malone  
F. J. Moran  
M. W. O'Connell  
H. C. Petterson  
S. A. Robins  
S. M. Saltz  
D. D. Scannell  
Nathan Sidel  
J. W. Spellman  
J. P. Treanor, Jr.  
W. J. Walton  
N. A. Welch

## NORFOLK SOUTH

C. S. Adams  
R. L. Cook  
F. W. Crawford  
W. G. Curtis  
J. E. Knowlton  
L. W. Pease  
D. B. Reardon  
H. A. Robinson  
W. L. Sargent

## PLYMOUTH

Charles Hammond  
P. B. Kelly  
P. H. Leavitt  
G. A. Moore  
W. H. Pulsifer

## SUFFOLK

A. W. Allen  
W. B. Breed  
W. E. Browne  
C. S. Butler  
G. C. Caner  
E. M. Chapman  
David Cheever  
M. H. Clifford  
N. W. Faxon  
Reginald Fitz  
Maurice Fremont-Smith  
Channing Frothingham  
Joseph Garland  
John Homans  
A. A. Hornor  
C. S. Keefer  
H. A. Kelly  
R. I. Lee  
C. C. Lund

H. C. Marble  
W. J. Mixter  
Donald Munro  
R. N. Nye  
F. R. Ober  
J. P. O'Hare  
W. T. O'Halloran  
L. E. Parkins  
L. E. Phaneuf  
Helen S. Pittman  
R. M. Smith  
E. F. Timmins  
S. N. Vose  
Shields Warren  
Conrad Wesselhoeft

## WORCESTER

J. C. Austin  
Gordon Berry  
W. P. Bowers  
L. R. Bragg  
L. M. Felton  
A. W. Marsh  
J. C. McCann  
J. W. O'Connor  
R. S. Perkins  
W. C. Seelye  
R. J. Ward  
F. H. Washburn  
R. P. Watkins

## WORCESTER NORTH

H. C. Arcy  
E. A. Adams  
H. D. Bone  
J. J. Curley  
C. B. Gay  
J. C. Hales  
B. P. Sweeney

## APPENDIX NO. 2

## REPORT OF THE TREASURER

The treasurer has continued his investment policy, as in the past years, to protect the funds in his care, rather than, by taking greater risks, to seek larger interest returns. Hence interest income, in 1941, was moderate. From a study of investment policies of many different security portfolios, and from a study of results of many managed "investment trusts," a fair conclusion is that constant revision, vigilant supervision and wise foresight are essential in successful management of invested funds. These rules are important, as never before, when securities must be shifted promptly, as new conditions arise with startling rapidity, affecting values. Changes in the Society's investments, in 1941, have, in almost all instances, shown profits. Yet, looking ahead, the increasing threat, under war necessities, of dangerous inflation, and the deficit financing of our government for past years, are warnings to the Society, to spend thoughtfully and economically.

In 1941, Society revenues from resident dues were \$49,779. Other net revenues, from interest (not including Building Fund) \$4081; from sales, \$13; net from booths sold for annual meeting, \$1065; from nonresident dues, \$1671; from fellows in active service in Army or Navy, to receive the *Journal*, \$32; fees from examinations by censors, \$243; and finally, profits on sales of bonds, \$815;

together amount to \$7920 Hence, total revenues to the Society amount to \$57,699—the largest ever received

Building Fund received net income of \$1889, and profits from sales of securities, \$116 Both were added to the Fund which now totals \$62,075

Items of expense, in 1941, were larger, primarily because of bills for lawyers, first in connection with legislative activities, and secondly, for work in connection with the proposed Massachusetts Medical Service Corporation There are, the treasurer believes, a number of other expenses which should be reduced in 1942 As many fellows of the Society have been called to active war duties with Army or Navy, and many more must soon be called, the Society will be without their presence, their advice and their dues We should strive therefore more than ever, with conscientiousness and economy to carry on the many activities and duties, now placed on our shoulders

The Society ends 1941, with assets of cash and securities, totaling \$216,800, and unexpended revenues of over \$12,300

The treasurer takes this opportunity to thank the officers of the Society, the officers of District Societies, and, especially the office staff of the *New England Journal of Medicine*, for their continued co-operation and help

CHARLES S BUTLER, Treasurer

## APPENDIX NO 3

### REPORT OF THE EXECUTIVE COMMITTEE OF THE COUNCIL

The president of the Massachusetts Medical Society, Dr Frank R Ober, on December 7, 1941, sent a message to His Excellency, Leverett Saltonstall, Governor of Massachusetts, pledging the support of the Massachusetts Medical Society in the crisis which had arisen that day

The following letter was received from the assistant secretary to the Governor

December 17, 1941

Dr Frank R Ober, President  
Massachusetts Medical Society  
8 Fenway  
Boston, Massachusetts

Dear Dr Ober

Governor Saltonstall asked me to thank you for transmitting to him your organization's pledge of support and patriotic offer of assistance Will you please convey to the members his appreciation?

He feels that it is such spirit that will pull us through the grave struggle ahead There are many vital tasks to be accomplished involving all the ability and effort we can muster Through various channels many groups are already enlisted for specific jobs and if such is not yet the case with yours, you may be assured that the call will soon come

Sincerely yours,

RUSSELL GFOULD  
Assistant Secretary to the Governor

The Executive Committee, at its meeting December 29, 1941, approved this act of our president. I now move that this act be likewise approved by the Council of the Massachusetts Medical Society

At this same meeting the Executive Committee took notice that our country was at war This notice took the form of a resolution which the secretary of the Massachusetts Medical Society was directed to send to the President of the United States

The following telegram embodying this resolution was sent on December 30, 1941

Honorable Franklin D Roosevelt  
President of the United States  
White House  
Washington, D C

I have been directed by the Executive Committee of the Council of the Massachusetts Medical Society to submit to you the following resolution adopted in Boston, December 29, 1941

Whereas, the liberties of all peoples are seriously threatened,

Whereas, these liberties no longer exist in a large part of the world,

Whereas, contagion threatens the spiritual as well as the physical things of life,

Whereas, personal freedom, the right of free speech, the right of peaceful assembly and the right to worship God, as one's conscience dictates, comprise the American way of life, and

Whereas, the Massachusetts Medical Society has nourished this American way of life for over one hundred and fifty-eight years, therefore, be it

Resolved, that the Executive Committee of the Council of the Massachusetts Medical Society, truly representative of 5600 physicians in the State of Massachusetts, pledges its treasure, skills, loyalty and, if need be, the lives of its several members to the President of these United States and may God keep him strong

MICHAEL A TIGHE, MD, Secretary  
Massachusetts Medical Society

The following acknowledgment was received from M H McIntyre, Secretary to the President

THE WHITE HOUSE  
WASHINGTON

January 3, 1942

My dear Dr Tighe

The President has received your fine telegram embodying the resolutions adopted by your committee and he wishes me to convey his deep appreciation of the patriotic support which you so generously pledge It is extremely heartening to the President, in carrying out the will of the American people, to receive the voluntary assurances that the country stands as one man in its determination to spare no effort and to assume every sacrifice necessary to a successful outcome

Very sincerely yours,

M H MCINTYRE  
Secretary to the President

Dr Michael A Tighe, Secretary  
Massachusetts Medical Society

The Executive Committee reviewed certain reports which will be presented today under the direction of the Committee on Public Relations The first of these has to do with tax supported medical care. This report involves the adoption of certain principles which have been evolved as the result of the studies of the special committee assigned to this subject

The second concerns itself with certain recommendations six in number, which will be presented today as the result of the further efforts of the Special Committee on Prepayment Medical-Care Costs Insurance.

The Executive Committee has approved these reports and recommends them as deserving of your earnest consideration.

The Executive Committee has approved of a third matter which will be presented by the Committee on Public Relations. This has to do with an attempt to solve a vexatious matter which has arisen in certain communities out of hospital-care insurance as applied to ward patients. If the Massachusetts Medical Service Corporation is to include those who will be cared for under a similar contract covering medical-care costs, this matter must be adjusted. The Executive Committee approves the recommendations of the Committee on Public Relations looking toward this end, and urges its adoption by the Council.

The following resolution is presented for adoption by the Council:

WHEREAS, It has come to the attention of the Council of the Massachusetts Medical Society that the Social Security Department of the United States Government seems to contemplate a petition to the Congress of the United States for legislation which would extend the present social security coverage so as to include approximately 45,000,000 to 116,000,000 of the American people;

WHEREAS, It seems to be the intention of the petitioner to have included in this legislation an extension of the provisions of the present Social Security Law so as to provide for the hospitalization of approximately 45,000,000 to 116,000,000 American people;

WHEREAS, It seems to be the intent of this legislation to finance this extension, in the case of the employed, by a tax of one per cent on payrolls, one half of which is to be paid by the employer and one half as a deduction from wages;

WHEREAS, In the case of those who are self-employed, it has been intimated that it will be the intent of this legislation to finance this extension by adding to already existing income taxes an additional tax of one per cent up to an amount which will represent one per cent of \$3000;

WHEREAS, The people of these United States are now heavily burdened and will be further burdened by our war effort;

WHEREAS, This is the first step in the direction of the complete control of the care of the sick by Government; and

WHEREAS, Wherever such control has existed the quality of medical care has suffered; therefore, be it

RESOLVED, That the Council of the Massachusetts Medical Society in regular session, February 4, 1942, does hereby oppose any such extension of the present Social Security Law as is herein outlined.

MICHAEL A. TIGHE, *Secretary*

#### APPENDIX NO. 4

##### REPORT OF THE COMMITTEE ON MEMBERSHIP

The committee recommends:

1. That the following named twenty-three fellows be allowed to retire as of December 31, 1941, under the provisions of Chapter I, Section 5, of the by-laws:

Abbe, Elizabeth M., Roxbury  
Atwood, Charles A., Taunton  
Brown, Percy, Egypt  
Burton, Oscar A., Westminster, Vermont

Coffin, Arthur B., Dorchester  
Devere, Frederick H., Auburn, Rhode Island, with remission of dues for 1940 and 1941  
Everett, Frederick L., Springfield, with remission of dues for 1939, 1940 and 1941  
Grandison, Wilfred G., Charlestown  
Hamilton, Robert D., Newburyport, with remission of dues for 1940 and 1941  
Harriman, Cora E., Framingham Centre  
Holmes, May S., Orleans, with remission of dues for 1941  
McIntire, Herbert B., Cambridge  
Morrison, Robert F., Holyoke  
Myrick, Hannah G., Dorchester  
Noble, Mary G., Brookline, with remission of dues for 1940 and 1941  
Parker, Ralph W., Lowell, with remission of dues for 1940 and 1941  
Rumrill, Samuel D., St. Petersburg, Florida, with remission of dues for 1939, 1940 and 1941  
Spalding, Fred M., Boston  
Spalding, Roger, Duxbury  
Wheeler, Lucia A., Uxbridge  
White, Clifford A., Granville  
Wood, Henry A., Waltham, with remission of dues for 1941  
Wylie, Eugene C., Dorchester Centre, with remission of dues for 1939, 1940 and 1941

2. That the following named seven fellows be allowed to resign as of December 31, 1941, under the provisions of Chapter I, Section 7, of the by-laws:

Bonnar, James M., Fairmont, West Virginia  
Brown, Manning, Hopkinsville, Kentucky  
Coggeshall, Howard C., Dallas, Texas  
Prout, Curtis T., Arlington  
Ragsdale, L. V., Grand Rapids, Michigan  
Segal, Jacob A., Manchester, Connecticut  
Woodbridge, Philip D., New Haven, Connecticut

3. That the dues of the following named ten fellows be remitted under the provisions of Chapter I, Section 6, of the by-laws:

Bartlett, Bernice A., Bradford, 1939, 1940 and 1941  
Bond, Katharine E., Melrose, 1939 and 1940  
Flagg, H. Howard, Charlestown, 1942  
Kaye, Edward, Dunbar, Virginia, 1940, 1941 and 1942  
Moore, Carlton W., Liberia, Africa, 1940, 1941 and 1942  
Perrault, Gerard R., Nashua, New Hampshire, 1940 and 1941  
Ryan, James B., 1939, 1940 and 1941  
Sanders, Morris B., Unoccupied France, 1941 and 1942  
Smith, Fannie G., Malden, 1941  
Wilder, Edward W., South India, 1940, 1941 and 1942

4. That the following named thirty-three fellows be deprived of the privileges of fellowship under the provisions of Chapter I, Section 8, Clauses *a* and *b* of the by-laws:

Atkinson, Velma H., New York City  
Barnes, Louis D., Pittsfield  
Bolger, Mary E., Worcester  
Calkins, Cheney H., Springfield  
Coon, George B., Greystone Park, New Jersey  
Fraser, John A., Somerville  
Garoyan, Gaspard M., Belmont  
Hall, Charles F. A., Newburyport  
Healy, John F., Dorchester

Klapper, Claude, Staten Island, New York  
 Lane, John W., Dorchester  
 Macaulay, Joseph A., Dorchester  
 Marcellino, Samuel E., Milton  
 McCarthy, Robert J., Malden  
 McClintock, Francis B., Chelsea  
 McCready, Leo T., Jamaica Plain  
 Mintz, Samuel C., Brookline  
 Monahan, David T., Bridgeport, Connecticut  
 Northridge, Robert J., DeLand, Florida  
 Oatman, Jack G., Fort Bragg, North Carolina  
 Oberlander, Andrew J., Montpelier, Vermont  
 O'Brien, John F., Bedford  
 Peacock, George E., Tuscarora, Pennsylvania  
 Quigley, Thomas J., Boston  
 Quinby, Robert S., North Sandwich, New Hampshire  
 Roney, Hugh B., Pittsfield  
 Savignac, Eugene M., Detroit, Michigan  
 Shadman, Alonzo J., Forest Hills  
 Sullivan, Jeremiah, Fall River  
 Toohy, Thomas V., Roxbury  
 Towle, George P., Carlisle  
 Vestal, Tom F., Raleigh, North Carolina  
 Zonn, Seymour I., Naugatuck, Connecticut

5 That the following named ten fellows be allowed to change their membership from one district society to another without change of legal residence, under the provisions of Chapter III, Section 3, of the by laws

From Essex North to Norfolk  
 Lary, Alfred J., Lawrence

From Hampshire to Hampden  
 Whitcomb, Austin E., South Hadley Falls

From Middlesex South to Norfolk  
 Doherty, John L., Newton Centre

From Middlesex South to Suffolk  
 Barney, J. Dellinger, Cambridge  
 Rabinowitz, James I., Cambridge  
 Sprague, John S., Brighton

From Norfolk to Suffolk  
 Davies, John A. V., Brookline  
 Marlow, F. William, Jr., Brookline  
 Tobey, Harold G., Jamaica Plain

From Norfolk South to Middlesex South  
 McKeon, Clementine C., South Hingham

6 That the following named six fellows be recommended for readmission under the provisions of Chapter I, Section 10, of the by laws

Bassow, George W., Winchendon  
 Bianco, Harvey H., North Adams  
 Burckel, Arthur W., Adams  
 Fallon, Joseph D., Northampton  
 Hannigan, R. C., Amesbury  
 Nicol, P. H., Worcester

G COLKET CANER, *Chairman*

## APPENDIX NO 5

### REPORT OF THE COMMITTEE ON FINANCIAL PLANNING AND BUDGET

The budget this year is made in anticipation of a considerable reduction in the collection of annual dues. The

Council is aware that the dues of those fellows entering the military services will be remitted on request. Thus, if one thousand fellows enter the military services, ten thousand dollars of income may be lost. Nevertheless, your committee has held that the activities of the Society should not at present be curtailed. The situation next year will be far more clear.

Taking the items of the budget in order, as presented, the following observations are pertinent.

The reduction in the salary of the secretary, tentatively suggested by your committee last February, in view of the possible lightening of his duties through the creation of the office of Executive Secretary, was approved by you. Since then, an executive secretary has been chosen by your Executive Committee. But the lightening of the duties of the newly elected secretary has not occurred. Dr. Tighe's enthusiasm, energy and capability have led him to devote a great deal of time to his office, and the committee in charge of the budget understands that he finds the delegation of such duties as he might technically be allowed to assign to the Executive Secretary improper and not in the best interest of the Society. Therefore, your committee feels that a salary of \$3000, that paid the late secretary, is appropriate.

The salary of the Executive Secretary, as tentatively suggested and approved last year, has been adjusted in conformity with the above. Mr. Boyd, appointed by your Executive Committee, though relieved of some of his expected duties, as stated above, does, in fact, give practically his entire time to the Society, has served various committees with success and, as the Committee of Arrangements can tell you, has actually, by the development of commercial exhibits, made the Society's annual meeting decidedly profitable.

Your committee is aware that the duties of these two officers are likely to develop and change during the next few years in ways which cannot at present be foreseen. Therefore, it holds that these proposed salaries, as presented in this budget, need not be regarded as fixed precedents and should be scrutinized from time to time with a view to adjustment.

The allowance for expenses of the Society's officers is nearly unchanged. That allotted to the President and Vice President should cover, as well, the expenses of a president-elect. The sum indicated here is really a contingent fund and has seldom been used to any extent. If emergencies call for greater expenditures, the Society's by laws permit proper arrangements to be made. The Secretary's allowance is increased.

The expenditures of certain standing committees will be slightly different this year from those of last year. The Committee of Arrangements is allotted only \$100. As already explained, this committee actually makes a profit.

The Committee on Publications includes in its activities the publication of the *Journal* and the *Directory*. It has presented this year, under the system established last year, a carefully considered budget. You will notice that the *Journal*'s allotment, stationary for three years, is now actually decreased. Dr. Nye and his staff have so ably conducted their publication that its cost, per member of the Society, has been steadily lowered and its subscriptions from outsiders have been steadily increased. And though the cost of publishing the *Journal* will certainly rise next year, Dr. Nye and the Committee on Publications feel that subscriptions and advertising will cover additional expenses.

The *Directory*, may, if you so decide, be omitted this year but we call your attention to several considerations

The old directory is nearly useless; the material for the new one is ready and if not used will be wasted. If the publication is postponed a year, its expense will coincide with the biennial expense of the Committee on State and National Legislation, an undesirable event. Because of the biennial sessions of the Great and General Court, the Committee on State and National Legislation now incurs a considerable expense every other year. Last year, owing to the exceedingly long session, legal expenses were heavy. This is an off year and an allotment of only \$100 is proposed.

Among the special committees, two require consideration. The Committee on Public Relations was especially active last year over the insurance matter. The President anticipates less expense this coming year. Yet \$1000 should be made available, since some bills have necessarily hung over from last year.

The Committee to Revise the By-Laws, headed by Dr. Blaisdell, will require a considerable sum if the original plan of printing the corrected by-laws is to be carried out. But some seven hundred dollars were expended last year and Dr. Blaisdell has suggested a plan, which should satisfy the Council, by which certain changes and corrections will be printed at an expense of not over \$300, the amount recommended

The total budget is \$50,800, a sum \$1000 less than last year, and \$3500 less than two years ago.

ERNEST L. HUNT  
CHARLES F. WILINSKY  
EDWARD J. O'BRIEN, JR.  
PEER P. JOHNSON  
JOHN HOMANS, *Chairman*

\* \* \*

The following budget is submitted:

REPORT OF BUDGET FOR 1942

SALARIES	
Secretary	\$3000
Executive Secretary	3000
Treasurer	2000
EXPENSES OF OFFICERS AND DELEGATES	
President and Vice President	500
Secretary	1800
Treasurer	400
District treasurers	2700
Censors	750
Delegates to House of Delegates, A. M. A.	400
Maintenance Society Headquarters	4500
Shattuck Lecture	200
Cotting Luncheons	450
Executive Committee	125
STANDING COMMITTEES	
Arrangements	100
Ethics and Discipline	60
Financial Planning and Budget	25
Medical Defense	2000
Medical Education	0
Membership	10
Permanent Home	0
Publications	
<i>New England Journal of Medicine</i>	20 000
<i>Directory</i>	2100
Public Health	25
State and National Legislation	100
SPECIAL COMMITTEES	
Committee to Examine WPA Records	5
Industrial Health	50
Maternal Welfare	150
Public Relations	1000
Postgraduate Instruction	1000
Committee to Revise the By Laws	300
Tax Supported Medical Care	50
RETURNS TO DISTRICT SOCIETIES	
	4000
Total	\$50,800

APPENDIX NO. 6

REPORT OF THE COMMITTEE ON PUBLICATIONS

The Committee on Publications has secured Dr. John F. Fulton, of New Haven, Connecticut, to deliver the Shattuck Lecture during the 1942 annual meeting of the Society.

The Committee has continued to supervise the publication of the *New England Journal of Medicine*. We are extremely fortunate in having such an able editor as Dr. Robert N. Nye. Under his direction, the high quality of the *Journal* has been maintained and the circulation has continued to show a gratifying increase.

RICHARD M. SMITH, *Chairman*  
JAMES P. O'HARE  
CONRAD WESSELHOEFT  
WILLIAM B. BREED  
OLIVER COPE

APPENDIX NO. 7

REPORT OF THE COMMITTEE OF ARRANGEMENTS

At the last Council meeting, you approved the following recommendations: (1) that the annual meeting of the Council be held on the evening of May 25, 1942, and (2) that the annual meeting of the Massachusetts Medical Society be held on May 26 and 27, 1942 at the Statler Hotel, Boston. Your committee has made those arrangements. A program, detailing the various activities, will be in your hands at the proper time.

The meeting will be larger than ever, but the cost to the Society will be less than ever. It is hoped that the program will merit your approval and support.

WILLIAM T. O'HALLORAN, *Chairman*

APPENDIX NO. 8

REPORT OF THE COMMITTEE ON ETHICS AND DISCIPLINE

The committee has held three full-day meetings during the past eight months, at which many cases were discussed. These cases fall naturally into four groups:

*Group No. 1*—numerous questions submitted by fellows as to the ethical nature of proposed publications. These requests were discussed and the proposed publications read, and decisions were handed down, some for and some against, to the satisfaction of the questioners.

*Group No. 2*—complaints received against fellows for alleged advertising contrary to the Code of Ethics. The complaints comprised radio announcements, newspaper publications and, in one instance, personal solicitation. These cases were investigated, and the committee found the fellows guilty as charged. All the accused fellows acknowledged their fault, sent letters of apology to the committee and promised to desist in the future. The apologies were accepted, and the cases placed on file pending further accusations.

*Group No. 3*—numerous complaints against fellows by private individuals claiming exorbitant charges for medical services. These cases were investigated, and in each, the physician was exonerated and both parties so notified.

*Group No 4*—two complaints by fellows against fellows charging violation of Article IV of the Code of Ethics of the Massachusetts Medical Society. After numerous conversations, correspondence and thorough discussion, the committee in both instances found for the plaintiff. The defendants were so notified. Personal apologies were received in both cases, the complaints withdrawn and the cases considered closed.

Several other matters are now under investigation including two communications from the office of the American Medical Association.

WILLIAM J BRICKLEY  
ALLEN G RICE  
FRED R JOUETT  
ARCHIBALD R GARDNER  
RALPH R STRATTON, *Chairman*

## APPENDIX NO 9

### REPORT OF THE COMMITTEE ON MEDICAL EDUCATION

This committee finds its effectiveness seriously impaired by the departure of one of its members on war service. Dr John Monks left last December to enter the United States Navy. Your chairman feels that the Society owes a debt of gratitude to Dr Monks for his faithful and intelligent service. He was particularly active. He led in a study of the by laws which resulted in rephrasings that have improved their interpretation and application. He spent a great deal of time investigating the qualifications of applicants for fellowship. Also, he had begun the collection of data showing the changes that have taken place in the membership of our society in the past ten years. The material is incomplete, but he has requested that some of it be reported at this time to focus attention on certain problems that may confront us.

The membership of the Massachusetts Medical Society has grown from 4750 to 5676 in the past ten years. This is an increase of almost 20 per cent. It is a more rapid rate of increase than in previous decades. Yet the number of applicants who become fellows and are graduates of approved medical schools has fallen off sharply in the last two years. From 1932-1939, they varied from 200 to 230 annually. In 1940, they fell to 179, and in 1941, to 115. The reason for this is not clear. Perhaps the war has much to do with it. If the decline persists, it merits careful study by the Council. During this same decade, the number of graduates of unapproved domestic schools entering the Society has remained essentially unchanged—22 to 38 in each year. The number of graduates of foreign medical schools rose from 4 or 5 through 1939 to 28 in 1940 and 60 in 1941.

Perhaps a measure of the efficiency of the Committee on Medical Education would be a comparison of the number of applicants for fellowship with the number who actually become fellows, for very few whom the committee passes are rejected by the Censors. In the last four years 95 per cent, 96 per cent, 88 per cent and 89 per cent of applicants from approved medical schools became fellows. During these same years, 40, 46, 40 and 32 per cent were accepted from unapproved domestic schools, and 30, 26, 42 and 66 per cent were accepted from foreign medical schools. These figures show that considerable care is exercised by the committee.

As a result of much study and consultation with various officials of the Society, this committee has unanimously approved the sense of the following:

1 Admission to fellowship in the Massachusetts Medical Society seems to be working out more satisfactorily under the new bylaws than under the old, although it is too early to be definite on this point. Members of the committee who served under the old rules are relieved to be free of the responsibility of selecting fairly among a great number of candidates on the basis of letters and casual personal interviews. This responsibility is now delegated to officers of each district society for the relatively few applicants in their area. As they become accustomed to their duty, the committee hopes that they will come to depend upon the confidential nature of the work and upon frank and convincing characterizations of their applicants. The committee then reviews the evidence of each man and determines whether it is sufficient to accept or to reject him or whether to advise deferment. More important, the committee equalizes the treatment accorded the candidates, for it is obvious that some districts will have strict and conscientious officers and others may have more lenient officers.

2 The committee should be allowed to continue to exercise its discretion in the approval of candidates. Only in this way can similar treatment be accorded candidates all over the State, based on one set of rules interpreted in the same way in each instance. By and large, however, there have been very few cases in which the decisions of the district society officers were reversed.

3 The committee is convinced that the Council would commit a grave error if it tried to increase by law or by interpretation the length of time necessary for a reputable foreign physician to be resident in this country or in one particular community before being allowed to apply for fellowship in the Society. If the present interpretation—five years since graduation from medical school—is retained, the committee assumes the responsibility of applying the law in the best interest of the Society and in fairness to the applicants. If a more rigid interpretation is compelled, unfairness clearly will result in special instances. Such rigidity conjures up unhappy attempts to go farther and define what is meant by the practice of medicine (bacteriologists, pathologists and so forth), what is the United States (Hawaii, Porto Rico, the Philippines), and what is a community (a district society area or a town).

4 The number of poorly educated graduates of unapproved domestic medical schools who enter the Society is too great. It appears to be due in large part to the considerable efforts on the part of a few fellows to do their best for their personal friends.

ROBERT T MONROE, *Chairman*

## APPENDIX NO 10

### REPORT OF THE COMMITTEES ON PUBLIC HEALTH AND MEDICAL EDUCATION

A joint meeting of these committees was held on January 15, 1942, to consider the advisability of continuing the weekly broadcasts of the Green Lights to Health. It was brought out at this meeting that the morning quarter of an hour now allotted to this program is much less satisfactory than that in the afternoon formerly given to it, limiting the audience largely to housewives. The

station has also imposed certain restrictions on the subject matter of the broadcasts. The field of obstetrics has been ruled out, although formerly we always had one broadcast each year on this subject. No mention is permitted of any such body functions as bowel movements, menstrual periods and so forth. This has limited the scope of the talks and made them less effective.

With so many physicians entering service and with increased demands on the time of the others, the committee felt that they were not justified in calling on members of the Society to give of their time in preparing broadcasts, where it was so difficult to get definite evidence that we are accomplishing enough in health education to justify the effort. The committee voted unanimously to discontinue the broadcasts on the completion of the present program about March 1.

FRANCIS P. DENNY, *Chairman*

## APPENDIX NO. 11

### REPORT OF THE COMMITTEE ON CANCER

The *Cancer Manual for Practitioners* has met with a considerable degree of enthusiasm and copies have been purchased for distribution to the practitioners of New Hampshire and Oklahoma. Several other states are interested in it also.

The desire of the Women's Field Army to put on an intensive campaign in Massachusetts was discussed, and although the committee was sympathetic in principle to the aims of the Women's Field Army, it seemed, after careful discussion, that no change in the present situation was warranted, and that the Society should not be asked to support a campaign by the Women's Field Army at the present time.

The matter of the reportability of cancer cases was discussed. It was felt that it would provide interesting and somewhat useful data. However, the committee feels that compulsory reporting of cancer cases is not advisable because of the opposition of patients and the fact that reporting must be by name to avoid duplication. In addition, it must be remembered that the reporting of diseases is an integral part of the police power of the Department of Public Health and, as such, should be restricted to those diseases dangerous to public health. Reporting of cancer morbidity was attempted by New Hampshire, found unworkable and abandoned.

The excellent work of the state-aided cancer clinics throughout the Commonwealth is known to the majority of practitioners. These clinics have been established with the active co-operation of the practitioners in a given community and serve as striking examples of how enthusiastic co-operation between the medical profession and the public-health authorities may react to the great benefit of patients. The Massachusetts system has aroused great interest in other parts of the country, and the Massachusetts cancer program is regarded as the most satisfactorily functioning program now in operation.

In view of the fact that the Society has a very real interest in these cancer clinics, and in view of the fact that such a move would be welcomed by the public-health authorities, it is recommended that a representative of the Society, preferably a member of the Cancer Committee, be appointed by the President to visit the various

state-aided cancer clinics and report to the Society on their present state.

F. G. BALCH  
E. M. DALAND  
C. C. SIMMONS  
P. E. TRUESDALE  
SHIELDS WARREN, *Chairman*

## APPENDIX NO. 12A

### REPORT OF THE COMMITTEE ON PUBLIC RELATIONS

1. The committee has given preliminary consideration to a "postpayment" plan for medical care sponsored by the banks and now utilized by the Massachusetts Dental Society. We recommend that the President be authorized to appoint a committee of three from the Massachusetts Medical Society to confer with the bank committee about this plan and report to the Council through the Committee on Public Relations.

2. The Committee on Tax-Supported Medical Care has formulated a set of principles and proposals. These have been carefully considered by the Committee on Public Relations and we now recommend their adoption. You have received printed copies of this report. If the Council adopts these as its policy, they will be submitted to organized welfare associations for concurrent action. After this is accomplished, the material will go to the local administrators of public medical care. The district medical societies have already been urged by this council to have their committees on public relation or a special committee apply and maintain steady but judicious pressure for better conditions and standards of public medical care.

3. We believe that insurance cases (Blue Cross, Workmen's Compensation cases, automobile accidents and prepayment medical-costs insurance) should be admitted to hospitals in the care of their physician of choice. About half the hospitals of this state now provide this "private ward" privilege. The practice is almost universal outside the Atlantic Coast states. We recommend that the Council instruct the Committee on Relations with the Massachusetts Hospital Association (Dr. Clute, chairman) to see whether there can be agreement on a state-wide policy in this matter.

4. The Committee on Public Relations has given major consideration to the setting up of the Massachusetts Medical Service Corporation. We feel that the Society is fortunate in having available for these studies James C. McCann, who combines capacity and the service motive to an unusual degree. He will present the report of the McCann Committee as adopted by the Committee on Public Relations.

E. S. BAGNALL, *Secretary*

## APPENDIX 12B

### REPORT OF SPECIAL COMMITTEE ON PREPAYMENT MEDICAL-CARE COSTS INSURANCE

Governor Saltonstall, on May 22, 1941, affixed his signature to an enabling act, which became a law of the Commonwealth, empowering the Massachusetts Medical Society to establish a nonprofit corporation for prepaid

medical care costs insurance. Basic principles incorporated in the act provided (1) for preservation of the traditional patient-physician relation which guarantees free choice of physician to the patient, and freedom of action with the proper restrictions of licensure, law and ethics, to the physician, (2) for participation in the program by all duly licensed physicians in the Commonwealth (3) for subscriber representation in the corporation by virtue of the quasi public character of the corporation and in recognition of a legitimate subscriber interest in such a program, (4) for supervision of the corporation by the Commissioner of Insurance so that the profession might properly discharge its serious moral obligation to conserve and protect potentially large accumulations of prepaid funds collected from the public.

In October, 1941, the Council voted approval of by laws which outlined a corporation devised to carry out the meaning of the enabling act, and to ensure fair and reasonable controls over the actions of the corporation in medical matters by the medical society which was to create and finance the corporation, and which was contributing the support of its membership to achieve its ends. These ends are to help alleviate the burdensome costs of medical care for the low income group, and to avert the threat of compulsory health insurance, or of compulsory reorganization of the medical profession into groups under lay or political domination.

Today, in February, 1942, the Council is requested to take definitive action on proposals, the acceptance of which will place us much nearer the achievement of our goal. We present these proposals at a time when the satisfactory financial condition of the Commonwealth will assure interest in our program by industry, trade and labor. We present it at a time when activities in Washington indicate that reformers again seek to inject government controls into the problem of medical care. Consider the announced program of nine points of freedom for the post war world, which, in article three, calls for adequate food, clothing, shelter and medical care, consider the annual message on the state of the Nation, calling for extension of hospitalization benefits to the unemployed, consider the proposal of the Social Security group that cash benefits and hospital expense funds be extended to all groups of the population while ill and unemployed, on the basis of extended taxation, consider that all such proposals are initiated and pressed by Falk and Altmeier of the Social Security Department, both public advocates of and propagandists for compulsory health insurance. Well may the profession be on the alert lest we suffer a Pearl Harbor in medicine, when our membership is deployed whilst giving unselfish service in the armed forces for defense of precious liberties which some within our very borders would abridge.

#### GENERAL OUTLINE OF PROPOSALS FOR EFFECTING INCORPORATION

Turning to the specific proposals on today's agenda, they seek to attain three objectives. The first group of proposals relate to several incidental measures necessary to complete the establishment of our corporation. These steps are as follows: co-ordination of our activities with the Associated Hospital Service group (Blue Cross), appointment of a special committee to select an executive director, authorization for procuring the services of an attorney for the special committee, and appropriation of \$75,000 as required by the Commissioner of Insurance. The second proposal relates to determination of income levels of eligibility for participation as a subscriber in the program. The third proposal seeks approval of the principle that complete medical coverage shall be gradually

approached through well defined steps of partial coverage. It would be trite to recall to this council that our last proposal of partial coverage as an initial step, asks for reversal of previous decisions made by this body. But it is well at this juncture for us to recall that the impact of world crisis has been adequate cause for the Supreme Court of our land to reverse previous decisions. I have no fear that the Council of the Massachusetts Medical Society will find itself so hidebound by previous decisions as to hesitate at reconsidering them in the light of new data and figures. I am confident that the Council will look to the cold logic of facts and experience for guidance, and that it will be influenced more by solid authority on what actually has been than by vapid theorizing on what might be.

#### PROPOSAL RELATIVE TO INCOME LIMITS OF ELIGIBILITY

The proposal relative to income limits of eligibility presents a fundamental and difficult problem. The proposal reads: That income levels for eligibility for medical service contracts (contrasted to medical indemnity contracts) be set at \$2000 for an individual and \$2500 for a family, estimated as average family income. At present only medical indemnity and not medical service contracts shall be offered above these levels.

First, we must have clearly in mind what we mean by the terms medical service contracts and medical indemnity contracts as relating to this proposal. We must once and for all eschew academic and pointless discussion relative to this distinction, and all futile argument as to whether or not this constitutes insurance. We must relate these two terms, for clarity's sake, to the practices we intend to carry out. Let us consequently discuss the practices and not sterile terminology. By medical service contract, we mean the practice of making available to subscribers, within predetermined income limits, contracts with the corporation on the basis of which they shall receive needed medical services of the types and amount designated in their contract, from a participating physician of their own choice, and that having received such medical services, the subscriber shall have no additional charges made to him by the physician other than such coinsurance or initial charges as are specifically enumerated in the policy—the physician in the transaction being compensated directly by the corporation on a unit basis related to an established fee schedule. The medical indemnity contract, on the other hand, indicates the practice of selling contracts by the corporation to those people with incomes above the designated level, who wish to avail themselves of some protection against the cost of illness. For the services enumerated in their contracts, the physician rendering service shall receive a specified amount from the corporation, this amount standing as a credit on the full charge presented by the physician who has in no way bound himself concerning treatment or charge by contract with this upper income group. The total charge by the physician for service to a subscriber in this category remains on a personal contractual basis between the patient and physician as it does at present. The subscriber stands personally responsible for the payment of the difference between the charge by the physician and the allowance by the corporation.

This brings us to the difficult problem of establishing specific income levels to which the two types of contracts shall be related. We must base our decisions in this matter on several interrelated factors. These factors may be identified as the general economic background of and wage levels in Massachusetts and those factors that have influenced previous decisions reached by ex-



isting medical-service plans under medical auspices in other states.

With reference to the first factor,—the economic background of Massachusetts,—the individual members of the Council have previously received a brochure entitled, "The Economic Basis for Prepaid Medical-Care Costs Insurance in Massachusetts." As the brochure was prepared hastily for the use of the special committee, there are a few basic charts which have since been more accurately calculated, and these will now be presented.

An adequate conception of the economic picture of the State is essential if we are to embark on an economic experiment of this magnitude on a state-wide basis. Otherwise serious misjudgments may be formed or ill-conceived actions taken. Massachusetts is basically an industrial state, with urban concentration of the population (Table 1). The census figures for 1940 indicate that the

TABLE 1. Percentage Distribution of Urban and Rural Population in Massachusetts (1940 Census).

REGION	1940	1930	1920
	%	%	%
Urban .....	86.1	90.2	94.8
Rural .....	13.9	9.8	5.2
Rural farm .....	2.9	1.9	1.6

distribution of the population is 86.1 per cent urban and 13.9 per cent rural. Of the latter group, only 2.9 per cent is bona fide rural farm settlement. Also an analysis of the occupational distribution of the population as wage earners may be had from a compilation based on the report of gainfully employed persons in the census of 1940 (Table 2). This chart was prepared by Mr. Joseph F.

TABLE 2. Occupational Distribution of Gainfully Employed Persons in Massachusetts (1939).

GROUP	NO. OF PERSONS	PERCENT-AGE
Manufacturing (wage earners).....	460,674	35.0
Manufacturing (salaried personnel).....	61,848	4.6
Wholesale and retail trade.....	262,467	19.8
Active proprietors of unincorporated companies (trade) .....	50,718	3.8
Public utilities .....	45,000	3.4
State, county and municipal (except schools) .....	85,000	6.4
Teachers .....	25,000	2.0
Service .....	41,000	3.0
Construction .....	38,353	3.0
All others* .....	249,940	19.0
Total .....	1,320,000	100.0
Unemployed .....	450,000	

\*Agriculture, professional, domestic, clerical, self-employed, federal and all other unclassified groups.

King, the statistician for the Department of Labor and Industry. As indicated by the chart, the group employed in industry represents between 30 and 40 per cent of the whole body of gainfully employed workers in the State. The percentage levels fluctuate from low to high, depending on the index of industrial production, at any given time. This, in turn, is influenced by such factors as depression, strike, lay-off, high or low investment, and, as at present related to the war, boom and depression. The next significant large employed group, but is approximately only half the size of the group, is the body of trade employees. This constitutes roughly 20 per cent of the wage earners

next several groups characterized by such activities as public utilities, state, county and municipal employees, teachers, services and construction encompass about 20 per cent of the wage earners, although each individually accounts for not more than 3 to 6 per cent of the gainfully employed persons. There is one very large unorganized group—the 19 per cent of unskilled workers—who will be difficult to reach with a program. These figures indicate immediately that the tactical approach must be toward the industrial groups, and toward such large single units as lesser classifications. With evolution of the present actuarial methods should be developed for the lesser classifications down to the ultimate of the individual. It is basic, however, that the smaller units are wholly desirable from an enrollment and percentage enrollment of the personnel is that this constitutes the safest form of actuarial method as far as distributing risk and diluting it against the corporation are concerned. Moreover, a 60 per cent enrollment in their individual units.

It is important to analyze the industrial units from the angle of size and geographic distribution of industrial units (Table 3). A fundamental fact is that of the 9007 industrial units in the state in 1941, only 900, or 10 per cent, are large (each employing 100 or more workers) and 75 per cent of the approximately 500,000 wage earners in the State. The remaining 85 per cent of the units are small (each employing less than 100 workers) that account for only 25 per cent of the wage earners. Our problem thus becomes one of numerical basis, the industrial groups being the objective, the trade groups our secondary objective, the other business classifications our tertiary objective. In the industrial group we must secure the co-operation of the large industrial units. The objective must rest on a factual basis, the location of these primary units. 8.5 per cent are located in the city of Metropolitan Boston, and 7 per cent of the remainder of Massachusetts. This distribution or localization of the geographic distribution of the wage earners themselves (Table 4). 19 per cent of them, and in the city of Boston) account for 67 per cent of the wage earners, — as against 14 per cent of the total. A secondary breakdown of the Metropolitan Boston area shows that industrial wage earners in Massachusetts accounts for 10 per cent of the total, but that the two cities of Boston account for 10,000 more than the city of Boston. The large group of industrial units is one of making an analysis from the viewpoint of the wage earners and physical location of industrial communities. What then, in the significance of the industrial units in the metropolitan area is the predominant factor in the cities of the metropolitan area.

h two thirds of the trade employees in the State Metropolitan Boston, according to Prof Richard P Doherty, of Boston University College of Business Administration, has a density of retail trade which is the highest in the Nation, being greater than that of New York City and that of thirty six states. The problem is thus further clarified. The wage earners in the heaviest employment category (the large industrial units outside Metropolitan Boston), the employees in the second employment category (the large trade units in Metropolitan Boston) and the workers in the

highest wage level as of September, 1941, was in the construction business (\$37 07 per week), and the lowest was in the retail trade group (\$22 11 per week). Other groups ranged between these levels. As strikingly different experiences in the weekly wage levels occur over a period of years as between the two major groups—industry and trade. The trade workers earned an average weekly wage of \$21 48 in 1939, as against \$23 75 in 1941, the industrial wage earner averaged a weekly wage of \$21 65 in 1939, as against \$30 62 in 1941. Thus the earnings of the trade

TABLE 3. *Relative Number of Workers in 9007 Industrial Establishments in Massachusetts (1941)*

NO OF WAGE EARNERS PER ESTABLISHMENT	NO OF ESTABLISHMENTS	NO OF WAGE EARNERS	PER CENT OF WAGE EARNERS	PERCENTAGE CITY OF BOSTON	GEOGRAPHIC DISTRIBUTION METRO POLITAN BOSTON	EXTRA METROPOLITAN AREA
1000 and over (2500+)	44	88 671		0	17 0	83 0
(1001 to 2500)	(9)	(32 865)				
	(35)	(56 006)				
501 to 1000	120	83 008		10 5	29 3	70 7
251 to 500	229	81 096		8 7	22 0	78 0
101 to 250	571	88 516	75	15 0	31 0	69 0
51 to 100	635	45 191				
21 to 50	1 173	38 451				
6 to 20	2 3 9	26 319				
1 to 5	3 421	9 222				
NO WAGE EARNERS	435	—	25			

large units of the third general employment category (the diversified classification) must be successfully attracted to enroll in any program for prepaid medical care. Without the support of these economic groups, and the support of a large segment of the medical profession of Massachusetts, any prepaid medical-care program is foredoomed to ignominious failure.

No definitive action on this problem of establishing income limits of eligibility should be taken until we couple the preceding analysis of economic establishments and

TABLE 4. *Relative Distribution of Industrial Wage Earners in Population Units in Massachusetts (1938)*

AREA	NO OF ESTABLISHMENTS	NO OF WAGE EARNERS	PERCENT AGE OF WAGE EARNERS	WAGES PAID
43 towns	801	69 470	19	\$73 104 911
39 cities	4 442	251 586	67	277 768 154
Boston (city)	2 255	54 160	14	64 003 058
Boston (Metropolitan)*	4 150	134 317	36	160 123 677
Towns and cities (extra Metropolitan)	3 348	240 899	64	255 357 487

\*Forty-two cities and 29 towns as follows—Boston, Cambridge, Chelsea, Everett, Lynn, Malden, Melrose, Newton, Quincy, Revere, Somerville, Waltham, and Woburn; towns—Arlington, Belmont, Braintree, Dedham, Canton, Cohasset, Dedham, Dover, Hingham, Hull, Lexington, Milton, Nahant, Needham, Norwood, Reading, Saugus, Stoneham, Stoughton, Swampscott, Wakefield, Walpole, Watertown, Wellesley, Weston, Westwood, Weymouth, and Winthrop.

the distribution of wage earners with a factual investigation of the annual earned wages of gainfully employed persons in Massachusetts. There is of course as wide a variation over several years in the wage levels, as there is in employment (Fig 1). In recent years the index number of wages has risen from the low figure of 58 in 1939 to the figure of 115 at the close of 1941. There is likewise a wide range in the wage levels in different occupational groups as of any given date (Table 6). The

worker tend to be stabilized at a median level during all phases of a business cycle, while the earnings of the industrial wage earner fluctuate widely over the cycle from a low of approximately the same median level to a decidedly higher level. The fluctuations in industrial wage pay are based not only on the rate of hourly wage, but also on the hours of employment. The recent increase of 40 per cent in the industrial wage level is due largely to overtime employment and overtime pay. Strangely this increase has been accompanied by an increase of only 65 per cent in the number of employed wage earners in industry.

A pertinent analysis of the specific annual earnings of workers in Massachusetts is available in a modified study by the Massachusetts Division of Employment Security, prepared by the Department of Research and Statistics. The basic chart has been modified with the help of Mr

TABLE 5. *Comparative Employment in Trade in 11 Leading Cities in Massachusetts (1941)*

CITY	ESTABLISHMENTS	NO OF WAGE EARNERS
Boston	776	79 640
Brockton	59	1 318
Cambridge	7	3 169
Fall River	87	1 594
Lawrence	51	1 434
Lowell	60	1 950
Lynn	53	1 439
New Bedford	70	1 548
Pittsfield	30	914
Springfield	127	4 209
Worcester	164	5 019

Joseph F King to suit the purposes of this study (Tables 7 and 8). Our deep obligation to Mr King for his valuable and generous contribution of time in this work should be recorded here. Table 7 is based on a statistical sampling of earnings reports as taken from the files in the Division

of Unemployment Security for 1939. The original figures were based on a sample of 30,525 reports. The groups earning from \$70 to \$400 a year were excluded from the revised chart here used, as they are constituted presumably of schoolboys, students in part-time employment, and

achievement of secure footing, these limits might properly be extended. Table 8 indicates that these figures apply to a group of wage earners of whom 95 per cent are employed throughout three or four of the quarters of the year. The importance of establishing the second or family

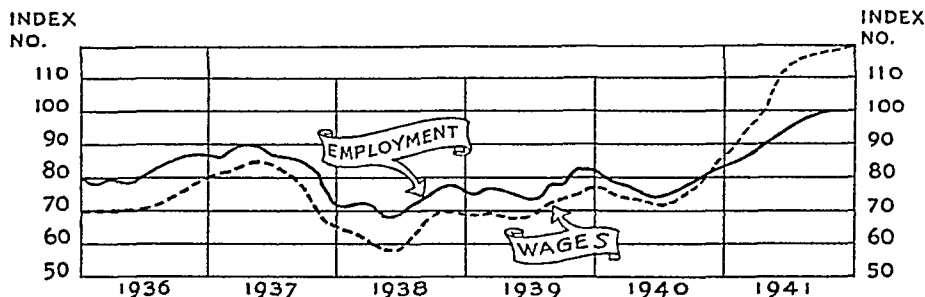


FIGURE 1. *Trend of Employment and Total Wages in Industry.*  
*This chart verifies the present high level of wages; the 1938 and 1939 levels are about normal.*

individuals with odd-time occupations who are not themselves interested in or capable of carrying full-time employment. The exclusion of these groups, which are not pertinent to our study, brings the sample down to 20,877, as shown in the table. The first eight blocks comprising the groups with earnings from \$400 to \$800 annually have, by action of the Wage-Hour Law enacted since the original study was made, been moved up into the group earning \$750 to \$800 annually. Such is the connotation of the word "corrected." The study shows that 25.7 per cent of a diversified group of wage earners in

level of eligibility is indicated by Table 9 which represents the experience of Blue Cross enrollment. Nearly half the semiprivate subscribers (48.1 per cent) and nearly three fourths of the ward subscribers (71.9 per cent) purchase hospital insurance contracts on a family basis, rather than on the basis of a smaller unit. A comparable

TABLE 6. *Analysis of Employment and Earnings in Massachusetts (September, 1941).*

GROUP	NO. OF WAGE EARNERS	TOTAL WAGES	AVERAGE WEEKLY WAGE
Manufacturing	459,580	\$13,966,299	\$30.39
Retail trade	73,445	1,624,102	22.11
Public utilities	48,455	1,744,871	36.01
Municipal employment	19,887	549,060	27.05
Wholesale trade	18,305	572,799	31.28
Construction	15,092	570,495	37.07
Miscellaneous classes	44,812	1,033,645	23.60

Massachusetts earned in 1939, \$750 to \$800 per year and that 14.9 per cent received \$800 to \$1000 per year. It is seen that 22.8 per cent received \$1000 to \$1500 per year; and that 20 per cent received from \$1500 to \$2000 a year. Thus it may be summarized that approximately 40 per cent of the wage earners receive from \$750 to \$1000 a year; that another 40 per cent receive from \$1000 to \$2000 a year, and that, of the remaining 20 per cent, a little less than 10 per cent (8 per cent) earn from \$2000 to \$2500 per year. If the income of the wage earners is taken as representing the total family income, then the proposed income level for eligibility of \$2000 for the individual (83.4 per cent of the wage-earning group) and \$2500 for the family (91.4 per cent of the wage-earning group) fairly discharges our responsibility to the low-income wage earner of the State in the initial stage of an experiment having potential magnitude of significant proportions. Interestingly, the comparable industrial state of Michigan adopted similar levels of eligibility, encompassing in Michigan 87 per cent of the workers at \$2000 and 93 per cent at \$2500. With the passage of time and the

TABLE 7. *Analysis of Annual Wages in Massachusetts (1939) Based on a Sample of 20,877 Diversified Wage Earners.*

TOTAL ANNUAL WAGE	NO OF WAGE EARNERS	PERCENTAGE	GROUP PERCENTAGE (WAGE-HOUR CORRECTION)	ELIGIBILITY PERCENTAGE
				\$2000 \$2500
400-450	901	4.23		
450-500	908	4.26		
500-550	914	4.30		
550-600	839	3.94		
600-650	791	3.71		
650-700	790	3.71		
700-750	828	3.88		
750-800	816	3.83		
750-800 (corrected)	6787		25.7	
800-850	786	3.70		
850-900	776	3.64		
900-950	726	3.41		
950-1000	656	3.08		
800-1000	9731		14.9	
1000-1050	639	3.00		
1050-1100	599	2.81		
1100-1150	550	2.58		
1150-1200	543	2.55		
1200-1300	1016	6.76		
1300-1400	970	4.56		
1400-1500	889	4.17		
1000-1500	5206		22.8	
1500-2000	2792	13.41	20.0	83.4
2000-2500	1440	6.76	8.0	91.4
2500-3000	953	4.17	5.2	
3000 and over	755	3.54	3.4	

experience might reasonably be anticipated among subscribers to medical-care insurance.

There are other factors which should be properly evaluated in arriving at a decision on this matter of income level of eligibility. They are quickly brought into focus by authoritative statements from other states which have

resolved this problem. There is shown in the second column of Table 10, the variations in the income limits of eligibility established by various states which have embarked on medical-care programs. In every state group,

TABLE 8. *Analysis of Total Time of Employment in Massachusetts (1939) Based on a Sample of 20,877 Diversified Wage Earners.*

TIME EMPLOYED	NO OF WAGE EARNERS	PERCENTAGE
One quarter	99	0.47
Two quarters	948	4.54
Three quarters	2,415	11.61
Four quarters	17,415	83.38

there is a minority viewpoint which holds that no income limitation should be established. Only Medical and Sur

TABLE 9. *Blue Cross Experience in Type of Care and Coverage of Hospital Contracts.*

TYPE OF CARE	PERCENTAGE INDIVIDUAL COVERAGE	PERCENTAGE HUSBAND AND WIFE COVERAGE	PERCENTAGE FAMILY COVERAGE
Semiprivate Ward	27.6 14.4	21.3 13.7	48.1 71.9

gical Care, Incorporated, of Utica, New York, has established itself on this basis. All other major groups have elected to establish income levels of eligibility. New Jer

*Michigan Medical Service.* "The income limits for eligibility were chosen on the basis of a number of income studies which indicated the level of \$2000 for the individual and \$2500 for the family constituted the so-called 'comfort level' above which persons were able to make individual arrangements for medical charges. The limits were also approximately (slightly lower) the limit of \$3000 proposed in government legislation for the under-income group." Laux, J. D., *Executive Director.*

*California Physicians Service.* "In arriving at the income level of eligibility, there was naturally a great variety of opinions as to how high or low it should be. The one factor that perhaps had the greatest influence was the family net income provision in the bill that was at that time being strongly pushed in the legislature. This bill provided for compulsory health insurance for all people earning up to \$3000, therefore this base figure was used in the rules of California Physicians Service." Nelson, J. Philo, *General Manager.*

*Western New York Medical Plan (Buffalo).* "In regard to the factors which influence the individual and family eligibility, would say that during the period of organization of the plan, there were two groups who held diverse opinions on this question. First, the majority opinion was that the income limits, or ceiling, should be very low. The minority view was that we should have no limits at all. The majority opinion prevailed, and the limits were set at \$1500, \$2000 and

TABLE 10. *Comparison of Major Medical Care Programs in the United States.*

PLAN	INCOME CEILING dollars	TYPE OF CONTRACT	PREMIUM dollars	REIMBURSEMENT CEILING dollars
Buffalo	1800 (individual) 2500 (couple) 3000 (family)	Comprehensive	18 00 (individual)	200
			27 00 (couple)	300
			36 00 (family)	400
		Surgical	4 80 (individual) 13 20 (couple) 20 40 (family)	150 150 (each) 150 (each)
Utica		Comprehensive	16 80 (individual) 13 80 (wife and each 16-18 yr old child) 9 00 (each 1-16 yr old child)	225 325 425
			10 00 (individual)	275
			9 00 (wife and each 16-18 yr old child) 7 20 (each 1-16-yr old child)	325 425
		Hospital (medical and surgical)		
New Jersey	2000 (individual) 2500 (couple) 200 (each child, to 3000 family limit)	Comprehensive	17.10 (individual) 31.35 (couple) 42.75 (family — 1 child)	
			48.75 (family — 2 children)	
			54.15 (family — 3 children)	
		Hospital (medical and surgical)	7 80 (man) 9 60 (woman)	
California	3000	Comprehensive	30 00 (individual, including 9 60 for hospital care)	
		Surgical	6 60 (individual)	
Michigan	2000 (individual) 2500 (family)	Comprehensive	24 00 (individual) 42 00 (couple) 54 00 (family)	325 375 150
			6 00 (individual) 15 00 (couple) 24 00 (family)	150 (each) 150 (each) 150 (each)
		Surgical		

sey Medical Service established a low level of \$1600, but for reasons unknown to the committee changed the limits to \$2000 for the individual, \$2500 for man and wife, and an allowance of \$200 for each child up to the income limit of \$3000. How the other major groups arrived at their figures is indicated by the following extracts from correspondence with them:

\$2500, respectively, for the three classes of subscribers — individual, man and wife, and family. When this plan was presented to the Insurance Department of the State, they demurred on the grounds that the limits were entirely too low, and at their insistence, they were raised to the present limits of \$1800, \$2500 and \$3000." Critchlow, George R., *Medical Director.*

There are further reasons why the committee suggests this simple approach on the basis of a flat level of individual and family incomes. The personnel managers of many organizations were polled and the opinion held by the majority of them indicated that their co-operation would be procured only to the extent that the society presented a simple basis of income eligibility for enrollment. Several organizations would refuse to divulge differing income levels among their employees; others would not set up the machinery for determining complicated and varying income bases for eligibility. If this responsibility devolved on the medical-service corporation, it would entail increased administrative expense. Industrial surgeons engaged in offhand conversation and queried, "What income limits encompass our problem?" replied, "About \$2000 to \$2500 for the family."

Proceeding on this simple base for enrollment, we can transpose the whole problem into an actuarial one, rather than establishing it on a complicated, unwieldy and poorly controlled enrollment basis. Because of these empirical reasons and the preceding statistical data, the committee has seen fit to recommend the same income levels of eligibility (or ceiling) as the comparable industrial state of Michigan, that is, \$2000 for the individual and \$2500 for the family, estimated as average family income. Above these income levels or ceilings, contracts will be available for the present only on a medical-indemnity basis.

#### PROPOSAL RELATIVE TO PARTIAL-COVERAGE OR COMPLETE-COVERAGE CONTRACTS

The next proposal entails complete reconsideration of all previous actions taken by the Council relative to the method of approach to the problem of prepaid medical care. The proposal reads, "That contracts be prepared and presented on the following basis: (1) the quick presentation of a so-called 'surgical contract' (coverage for the expense of hospital surgery, obstetrics and diagnostic x-ray service); (2) preparation, as quickly thereafter as is feasible, of a total hospital medical-care contract to cover all medical fields incidental to hospital medical-care expense; and (3) the careful, slow preparation of a comprehensive medical-care contract covering medical-care expense in the home, office and hospital, to be presented later."

Your committee urges a gradual approach to our ultimate objective and ideal—total medical-care coverage by a comprehensive policy—through well-defined initial steps of partial coverage. There are many reasons for not initiating our program with complete coverage, all of which may be summarized briefly as follows: complete medical-care coverage as the initial step in an extensive program has proved hazardous and frequently unsound; it has lacked widespread public acceptance by the low-income groups, the one true measure of public demand and interest; it has been subject to disrupting and ill-controlled abuses by the public in medical care at the office and home; and it has entailed either serious financial loss or inadequate compensation for the physician when unbuttressed by surpluses from more actuarially sound partial-coverage contracts.

It is well to realize that with the years of experimentation behind the profession, in which most initial ventures in other states were initiated with complete medical-care contracts, a survey of the breadth and length of this mighty land reveals only about 300,000 subscribers (exclusive of 450,000 in Michigan) to medical-care programs. Such a result will neither solve the problem of medical

costs for the low-income group, nor roll back the threatening wave of government control of private-family medical practice. The experiments have been of inestimable value as a source of information for developing sound, widespread, and publicly acceptable programs. However it seems that failure to proceed successfully at a faster pace in the future will prove futile and disastrous. Reformers wait neither on time nor doctors! This recommendation for initial partial-coverage contracts mirrors the findings of an earlier committee, the Subcommittee on Social Legislation Insurance of the Committee on Public Relations, which in 1938 recommended partial coverage for medical expense in the hospital only. Your present committee in effect resubmits its sound conclusions, following a survey of recorded experiences during the past five years in various sections of the country, and it furthermore presents support for such an initial partial-coverage step, by way of recommendations from outstanding authorities in the field.

Why should we consider charting a new course and rejecting total coverage as the initial step? The reason comes persuasively from the lips of Mr. John R. Mannix, who years ago was active with the Cleveland Academy of Medicine in formulating its plans, and is now director of Michigan Hospital Service and interlocked actively in administrative work with Michigan Medical Service. He writes:

The public is not yet ready to accept prepayment for complete medical care. The first prepayment plan was for hospital coverage in New Orleans, St. Paul and elsewhere in 1933. The movement started by offering hospitalization at 60 to 80 cents a month for the individual. The public took the attitude that there was not much to lose. Then the call on the budget was slowly increased to \$1.50 or \$2.00 a month for the entire family in 1936. When the Michigan medical-care plan for complete coverage was started, this meant a jump from \$1.50 per month for family hospital coverage to \$6.00 per month for family coverage of hospital and complete medical-care expense. The public is not ready to budget that much money. They must be led gradually to increasing budget contributions. The only ones who took the complete medical-care program were large numbers of people in groups which were known to need considerable medical care. Thus groups were selecting adversely against the program. As a consequence the complete medical-care portion of the program suffered a deficit of \$75,000.

It should be recorded here that it is Mr. Mannix's conviction that over the years the American people can be educated through the medium of partial-coverage contracts to budget the sums necessary for complete medical-care coverage.

Experiments with prepaid medical-care programs fairly well cover the Nation. When Massachusetts, venturing on a state-wide program, looks abroad to profit from experience elsewhere, she must use discrimination regarding sources whence conclusions are drawn. We have nothing to learn from a chain of small private group-clinics like the Ross-Loos organization in Los Angeles. Having rejected the basic philosophy of consumer dominated co-operatives in the field of medical care, there is but little to learn from the Elk City Medical Cooperative, of Oklahoma, in the heart of a producer and consumer farming co-operative country, or from the federally financed and nurtured Group Health Co-operative in Washington, D. C. Small medical plans in individual cities and in restricted geographic sections afford little dependable ex-

perience for such a venture as Massachusetts approaches. We must be particularly wary of the dependability of the many general surveys stimulated by the report of the Committee on the Costs of Medical Care (1928-1931). Many of these surveys seem to assume an unwarranted degree of accuracy. Michigan found that a survey estimate of eight hundred office calls per 1000 subscribers grew to the figure of three hundred office calls per 1000 in actual field experience and that the United States Public Health Survey estimate of a case rate of one mastoid and one hernia per 1000 persons per year, proved from field experience in Michigan to be two mastoids and four hernias per 1000 per year. Accepting the integrity of the bulk of the profession as a basic premise, we had better interpret this discrepancy as incidence of the absolutely restricted value of general surveys, rather than as evidence of unnecessary surgery. People are not fooled about mastoids or hernias at the rate of two to one and four to one. This may properly be interpreted as more adequate distribution of needed surgical care. The most valuable lessons for Massachusetts are to be derived from the states of Michigan, California and northern New York.

Having reviewed the empirical conclusions of Mr. Mannix, let us review his story of Michigan's actual experience with a complete medical-care contract. He writes:

The Michigan Medical Society and its Board of Delegates originally proposed and developed a program for complete medical care. The Ford Motor Company became interested as the first large subscriber but would not permit a deduction of \$6 per month for complete coverage of hospital and medical care for the family. They said they would only take surgical care. Such a contract had not been prepared or planned, and the Medical Society at first opposed partial coverage. Because of the insistence by industry, they then agreed to prepare a policy offering surgical, obstetrical and x-ray coverage, with the understanding that they would push the complete medical care policy and offer the partial coverage only where it was demanded. But they found that the public was not ready for an adjustment from \$150 for monthly family hospital coverage to \$6 a month for total family hospital and complete medical coverage. Despite all efforts, they could not get any interest in complete medical coverage even when they pushed it. At first they even had no folders on surgical coverage. But industry kept insisting. Why not talk about surgical coverage? In practice they have had to reduce complete medical-care coverage because of the abuse it was subject to. The abuse was in the home and office visits. The chief ones were in allergy and in pediatrics. A mother would come downtown with five healthy children and walk in on the pediatrician for examinations. The physician in this policy became as available as the nearest telephone. The Michigan Medical Society has lost \$75,000 on the complete medical-coverage plan, even though they had a deductible initial charge of \$5 which the patient paid.

Further evidence of the unsatisfactory Michigan experience with complete coverage is attested by the statement of Mr. Begley, assistant director of Michigan Hospital Service at a meeting of those interested in the medical plans in Atlantic City on September 16, 1941. He said:

They enrolled the entire Highway Department of the State of Michigan under a complete medical program, after a year's experience, the plan lost approximately \$10,000 on this one account. It had been determined that subscribers would use approximately eight hundred

office calls per one thousand subscribers, but in this one case subscribers used sixteen hundred office calls per 1000. The Michigan Medical Care Plan was not as successful as they had hoped.

In view of these enlightening revelations, how has Michigan Medical Service achieved its phenomenal success of over 400,000 subscribers, and participation by Michigan physicians to the extent of over 80 per cent in one year? They did this by responding realistically to the public demand in industrial Michigan with a partial coverage contract for surgery, obstetrics and x-ray service in the hospital. The public emphatically demonstrated their interest when at one period in the first year, it had bought over 187,000 surgical contracts and only 5816 complete-coverage medical contracts. Later in the year, General Motors participated in the plan to the extent of enrolling 250,000 subscribers. 82 per cent of these bought the partial-coverage surgical policies. On this contract, Michigan Medical Service has paid 100 cents on the dollar of the established fee schedule on the complete coverage contract. It has paid 70 to 85 cents on the dollar, but with a substantial deficit. During 1940, \$200,000 was paid to the physicians for services to subscribers. During 1941 over \$1,000,000 was paid, and at the present time payments to physicians approximate \$200,000 per month.

One matter of major importance from the viewpoint of our secondary objective of blocking compulsory health insurance is the rapid rate of enrollment in Michigan in one year (400,000 participants) in comparison with the 300,000 enrollees in all the other plans in the country over a period of years. Michigan has also dealt with one of the most strongly organized groups of union members in the country. In striking contrast with the demand of many labor leaders for compulsory health insurance, there stands the attested attitude of the individual members of the United Automobile Workers in Michigan that they sympathize with the doctors not wanting government in medicine and in the hospitals just as they themselves want to keep government out of the unions, and that so long as the physicians continue to provide a satisfactory arrangement for them for medical care, that will continue to be their attitude. Bearing out the achievement of Michigan Medical Service in reaching the low income groups which are not so effectively organized in unions as the automobile workers, is the fact that the best enrollment has been among the distinctly low income group. Kresge store girls get \$13.00 per week, and 92 per cent of these girls in the Kresge stores in Michigan are enrolled and there are 2000 of them. Mr. Mannix has the following to say concerning these girls:

They are self-respecting; they buy everything else, and they consider these rates within reason. The reason they previously went to the hospital as charity ward service cases was not that medical care was so expensive; they were not prepared to budget for the expense. There are relatively few families who cannot budget for medical care.

Further valuable information concerning experience derived from an extensive geographic area is available from California. In view of the gratuitous remark so frequently passed, that a complete medical-care program with an initial enrollment of 5000 to 10,000 people can successfully carry itself and properly compensate the physicians, the California experience with 30,000 subscribers is particularly enlightening. Mr. Mannix, of Michigan, reports

California offered complete medical-care contracts only, from 1939 onward for two years. After two years' experience with the complete medical-care contract, they were convinced that the complete program was not what the public wanted. Their monthly rates were \$4.50 for man and wife and two children and \$0.75 for every other child. Their complete contract was thus less expensive than Michigan's. With it they paid the doctors an average of 60c on the dollar. After two years they visited Michigan to get information about the surgical contract. Last August, they offered the surgical contract to the public.

Direct correspondence with the administrators of the California Physicians Service expands the basis for these assertions. A letter from Dr. Larsen, the secretary and medical director, contains the following illuminating remarks:

The trick in all of these medical plans is to get off on the right foot. Once you are in the game it is very hard to change around, and while you are doing so you lose both medical and public support. I am just throwing this out because I feel that this is the proper way to approach the development of a medical-service plan. . . .

There is no question but what the public *wants* full-coverage medical service rather than just the surgical benefit. Our figures to date . . . involving over 30,000 members . . . would lead us to believe that *the public is not yet prepared to pay the cost* that a full-coverage plan would require. We have gone into the full-coverage with complete knowledge of this, but we felt that some of these medical-service plans should find out just what the implications of full coverage under the free-choice service would actually mean in terms of dues and in terms of public reception. We believe that we are pretty close to the answer after two and one half years of experience. We have found that the full-coverage plan puts us into the white-collar class and does not get us the real low-income people. This has made for bad public relations as far as the medical profession is concerned, because a good number of our physicians feel that these people have been able to pay their bills previously. When you are confronted with a low-unit value, the doctor feels that he is losing money by taking care of this class of people.

A final statement with reference to the weakness of complete coverage as an initial approach for Massachusetts is contained in a letter, dated December 30, 1941, from J. Philo Nelson, general manager of California Physicians Service:

Experience under the full-coverage medical contract, in which all services, including the first visit, are taken care of, indicates a considerable amount of abuse on small insignificant ailments. This abuse is enough to have a definite influence on the payments that can be made for all services under the plan. California Physicians Service has now discontinued the sale of this particular contract, and in lieu thereof is offering a contract in which the member patient must pay for the first two visits in each ailment. Whether or not this restriction can solve the problem we shall not know until we have sufficient experience.

The questions now arise, Are we to profit by the experience of these existing medical plans, or are we going to blind our eyes to the very evident implication of

these results, and have to relearn the same costly lessons which these planners have concretely revealed? All of us who follow their lead are profoundly indebted to the physicians and lay associates in the various sections who have sacrificed time, effort and income that we who now must run, may profit by their more leisurely experience. Three striking facts are apparent from a survey of the field: most plans which started initially with a complete-coverage medical contract have been forced by public demand to fortify it with a partial-coverage contract; there is about an even division among these plans (Table 10) concerning which of two types of partial coverage is best added to the complete-coverage contract, that is, a hospital surgical, obstetrical and x-ray partial-coverage contract or a partial-coverage contract providing for all medical-care expense in the hospital; and there is definite feeling among these now experienced administrators that a state program, newly starting, might be well advised to initiate its program with a partial-coverage contract.

The opinion and the recommendation of your committee are that, profiting by these valuable experiments elsewhere, Massachusetts Medical Service be initiated on the basis of a partial-coverage contract. Our two objectives might be set as follows: to demonstrate to the many states that are becoming interested in voluntary prepaid medical-care programs and, like us, must profit from the experience of those that preceded us, how quickly and solvently such a program may be established on a state-wide basis; and to measure empirically the degree and extent of medical coverage and the premiums which the public will accept at present, and, as a corollary, the rate at which the public can be led voluntarily through partial coverage, to budget for complete medical-care coverage. The profession should not police the public to acceptance of specific types of medical coverage, any more than the government should. To this end your committee has recommended the immediate presentation of a partial-coverage contract providing for hospital surgical, obstetric and diagnostic x-ray benefits. This policy is actuarially sound; it represents the present limit to which the public gives evidence of participating voluntarily in large numbers; it will establish the corporation on a sound basis and create a reserve to buttress a more experimental total-coverage contract later. Within a short period of time after presenting the surgical contract, a contract covering complete medical-care costs in the hospital would be presented. This second policy would thus cover all the catastrophic medical expenses incidental to hospitalization. Then over a period of one or two years, a comprehensive medical-care contract covering medical-care expense in the home, office and hospital can be prepared, based on a further experience with this contract in other sections, and buttressed by a financial reserve accumulated with the actuarially sounder partial-coverage policies. The present committee would not assume the responsibility of preparing and presenting a complete-coverage policy within a shorter period of time than one or two years. As the committee senses a determination on the part of the Society to act immediately, there seems no rational alternative but to initiate the program on the basis of a partial-coverage contract.

The lessons of experience point this way as indicated by even a cursory examination. Conviction comes more completely by specifically seeking advice from unquestioned authorities on medical-care programs. The following excerpts from conversations or correspondence with such authorities leave little doubt as to the logic

of an approach through partial coverage for any statewide plan initiated from this time forward. Again I quote from Mr. Nelson, of California Physicians Service, who writes, "The surgical benefit contract is more or less predictable from an actuarial basis, and is the soundest one to begin with." This viewpoint is emphatically substantiated by a frank categorical statement by Mr. Mannix, 'From the experience of Michigan, partial coverage is the only approach that is reasonable.' He continued in an advisory tone that the recommendations of our committee were sound and that 'it would be well to go to the combination of hospital coverage with surgery, obstetrics and diagnostic x-ray, then to hospital coverage with complete medical-care coverage in the hospital, then hospital coverage with total medical care coverage.'

The next source I wish to quote from is an eminent, nonprofessional student of medical economics. I refer to Michael Davis, formerly a member of the Executive Committee of the Committee on the Costs of Medical Care and at present chairman of the Committee on Research in Medical Economics and editor of *Medical Care*, the quarterly publication of that committee. An expression of opinion by him on our specific problem deserves to be highly regarded. I quote him both from conversation and correspondence. The conversation can be presented only as my memory recalls it, and hence with the reservation with which recollected statement must be offered. In discussing the question of a partial coverage or a complete-coverage contract as the initial step in a program such as ours, he said that the only certain way of achieving a financially secure base with a complete-coverage contract would be by procuring the co-operation of an industrial establishment which would guarantee from the beginning the necessary 10,000 or more subscribers to a complete medical-care contract, which enrollment is estimated as the minimum figure which will stabilize such a contract financially. In correspondence with him, his full statement—the last sentence of which accepts the principle of an initial step by partial coverage—was as follows:

I believe that the medical profession ought to offer a scientifically designed medical service, utilizing the preventive and therapeutic powers of medicine. A plan under medical society auspices ought, therefore, to include general medical care and specialist service in minor disease and in the early stages of serious disease, as well as service for expensive catastrophic illnesses requiring hospitalization. You may, however, proceed with the aim of getting a prepayment plan promptly under way with enough membership to be self-supporting, rather than from the point of view of basic professional principles. Under such limitations, a service confined to the last named group of illnesses will usually be more salable to industrial workers, chiefly because, in their view, the rate will be lower and the sense of immediate protection stronger.

Where could one find a more lucid, precise statement of our objectives?

Finally, I quote several excerpts from letters received from Mr. R. F. Cahalane, executive director of Massachusetts Hospital Service (Blue Cross), who is in a strategic position to measure the interests and demands of individuals and organizations in Massachusetts. One letter remarked, "My only hope is that your committee can meet soon and as often as necessary to crystallize this whole

thing and get a surgical plan out to the public without delay." In another letter he stated "In our contacts with present subscribing groups and prospective groups we are running into some difficulties because of our lack of surgical coverage. Most of these groups openly admit the one reason for considering commercial groups is the surgical coverage, and everyone admits the superiority of the Blue Cross plans." Another statement was as follows:

Enclosed is another indication of the urgency of getting a surgical plan started. I am enclosing a letter from a subscriber, which was written in reply to a letter from us, inquiring why a subscriber cancelled. This subscriber appears very grateful to Blue Cross for all that has been done for him, but has taken a commercial contract because he can get surgical coverage. The number of instances where my men have occasion to report to me serious competition is rapidly increasing. A number of instances have arisen this week. The only competition exists because we are unable to offer a surgical contract. For this reason I am pleading for prompt action toward this end.

Finally I present a letter from Mr. Cahalane which indicates the reception our first partial-coverage contract will probably receive. He writes:

In getting the list of firms which indicated their interest in the surgical plan, which list was given to the Commissioner of Insurance, I find that a number of interesting answers were made to the question whether they were interested:

*Boston Consolidated Gas Company* Absolutely  
When is it coming?

*Converse Rubber Company* Mr. Berlin, president,  
'If Blue Cross supports and recommends it, we certainly will be interested.'

*Filene's* Mr. Bean, executive assistant, 'The sooner the better.'

*First National Bank of Boston* Mr. Brown, "Very much interested."

*Hood Rubber Company* Dr. Daniels, "Very much interested."

*Lever Brothers* Mr. Kelley, "Very urgent."

*New England Telephone and Telegraph Company*  
Mr. Weir, "Absolutely."

Mr. Spaulding contacted the Heald Machine Company, Norton Company and Whitin Machine Company (Worcester County). He received an O. K. from all of them. I do not have a record of just what the comments were in detail.

Mr. Cunningham made the contacts in Boston, and he reported general enthusiasm on the part of everyone. From this it would appear to me that there will be no problem in getting enrollment.

For these cumulative and convincing reasons your committee recommends (1) the quick preparation of a so-called "surgical contract" (meaning coverage for the expense of hospital surgery, obstetrics and diagnostic x-ray service), (2) preparation, as quickly thereafter as is feasible, of a total hospital medical-care contract to cover all medical fields incidental to hospital medical-care expense, and (3) careful, slow preparation of a comprehensive medical-care contract covering medical care expense in the home, office and hospital, to be presented later.

JAMES C. McCANN, Chairman



## APPENDIX NO. 13

## REPORT OF THE COMMITTEE ON POSTGRADUATE INSTRUCTION

The Society's postgraduate program began this fall with the New England Postgraduate Assembly, which was held October 29 and 30, 1941, in Sanders Theatre at Harvard University. The program was of wide medical interest. The following distinguished physicians made the assembly a notable success:

Dr. Frank E. Adair, New York City  
 Dr. J. Burns Amberson, Jr., New York City  
 Mr. J. J. Bloomfield, Bethesda, Maryland  
 Dr. William Darrach, New York City  
 Dr. John F. Fulton, New Haven, Connecticut  
 Dr. John S. Lockwood, Philadelphia  
 Dr. H. M. Marvin, New Haven, Connecticut  
 Dr. Wm. S. McCann, Rochester, New York  
 Dr. Damon B. Pfeiffer, Philadelphia  
 Dr. Homer F. Swift, New York City  
 Dr. George W. Thorn, Baltimore  
 Dr. Norris W. Vaux, Philadelphia

The assembly attendance by states was as follows:

Massachusetts	..	542
Maine	...	56
New Hampshire	..	31
Vermont	..	19
Rhode Island	..	37
Connecticut	..	14
New York	..	10
Others	..	11
Total	....	720

The finances were satisfactory as the receipts were \$301.41 more than the expenses; this result helps to balance the deficit of last year.

This year the postgraduate extension program has been organized in two divisions—a general course sponsored by the Society, for which there is a registration fee of five dollars, and a course in venereal disease financed by the United States Public Health Service and the State Department of Public Health, for which there is no registration fee. Both these courses are open to all legally registered physicians.

The postgraduate extension program started in Norwood on January 15. The general course will be given in the following places:

Berkshire	Pittsfield
Bristol South	Fall River
Hampden	Springfield
Hampshire	Northampton
Middlesex East	Winchester
Norfolk	Norwood
Norfolk South	Quincy
Worcester	Milford
Worcester North	Fitchburg

The course in venereal disease will be given in the following places:

Berkshire	Pittsfield
Bristol South	New Bedford
Norfolk South (two lectures)	Quincy

No extension program will be offered in the metropolitan area due to the large number of medical-defense courses.

Programs of the above courses were published in the *New England Journal of Medicine*, issue of January 15, 1942; folders giving full data concerning the courses

have been mailed to all registered physicians in the various districts. The committee wishes to express its appreciation for the continued co-operation and helpfulness of the State Department of Public Health.

At the present time the committee is studying the prospect for the New England Postgraduate Assembly for next fall; no final decision has been reached; a further report on this project will be made at the annual meeting.

The committee wishes to express the thanks of the Society to the instructors of the postgraduate extension courses and all those whose efforts helped to make the assembly a success.

REGINALD FITZ, *Chairman*  
 LEROY E. PARKINS, *Secretary*

## APPENDIX NO. 14

Franklin P. Lowry, M.D.  
 313 Washington Street  
 Newton, Mass.

February 3, 1942

Dr. Michael A. Tighe, Secretary  
 The Massachusetts Medical Society  
 8 Fenway  
 Boston, Massachusetts

Dear Dr. Tighe:

I shall be unable to attend the Councilors' meeting tomorrow.

The Committee on Physical Therapy has no definite report to make.

We do, however, have an occasional opportunity to enlighten organizations and individuals about the relative value of the several schools of physical therapy hereabouts.

Should Dr. Ober think best—if time permits—to announce the opening of the second Technicians' Six Months' Course in March, it might be possible that some of those present might know of prospects.

Cordially yours,  
 FRANKLIN P. LOWRY

## APPENDIX NO. 15

## REPORT OF THE COMMITTEE ON MEDICAL PREPAREDNESS

This committee has heretofore had no report to present to the Council. About January 1, however, it became obvious that the committee might soon be expected to play a part in helping out in the Procurement and Assignment Service for physicians in Massachusetts. Accordingly, the following letter was sent on January 9 to the President of each district medical society:

Dear Sir:

It is to be anticipated that the Medical Preparedness Committee of the Massachusetts Medical Society will soon be requested to assist the National Procurement and Assignment Service. It is planned to mobilize the entire medical profession in order to utilize this profession as effectively as possible during the duration of the national emergency. To help in the accomplishment of this, a survey in Massachusetts must be made in order to make it clear what are the medical needs of our community, civilian and industrial agencies, hospitals and so forth. There are enough physicians available to be of service to the Army without in any way neglecting our civilian population.

Committees should now be appointed by the president of each district society. The size of each district committee will vary with the size of the district society. If already a committee for preparedness exists in your district, it should be given the duty of the committee of which I write.

The purpose of such committees will be to study the number and capabilities of all physicians in their districts with a view toward helping to classify them into various groups, such as (1) suitable for military or naval service, (2) to be kept from military service because of being essential to the community, industry or defense work of any sort, (3) unfitted for military service but able to carry on civilian or hospital practice, and (4) unsuitable for any type of medical work because of age or physical infirmity.

My understanding is that such committees are to do nothing at present beyond organizing themselves in readiness to go to work when ordered to do so. This preliminary letter asks you to appoint such a committee as I have outlined in your district, sending to me the names of the men appointed. The size of the committee is left entirely to your judgment. Please ask each member of the committee to read the article which appeared in the December 6 number of the *JAMA*, pages 1983-1987. Make it very clear to each member of your committee that at present the committee is to do no more than make plans for operating when ordered to do so.

Yours sincerely,  
REGINALD FITZ, *Chairman*

The response to this letter was reasonably prompt. Already there have been appointed appropriate committees in the following district societies:

Berkshire	Hampshire
Bristol North	Middlesex East
Bristol South	Middlesex South
Essex South	Suffolk
Hampden	Worcester
Norfolk South	Plymouth

On January 24, the chairman of your committee received a letter from Mr. Paul McNutt concerning the Procurement and Assignment Service for physicians. Parts of this are quoted:

It is planned to have an advisory committee in each corps-area to assist this office in the carrying out of its functions. To supplement each corps-area committee it is planned to have a state committee. I should appreciate it if you would serve as the chairman of your state committee.

As chairman you will be expected to organize your state committee and to set up the necessary committees below the state level which will assist you in obtaining information relative to the availability of physicians in your state who may be asked to volunteer their services elsewhere in the interest of the national emergency.

The function of the state committee will be to coordinate surveys in each state and to assist in the determination of the assets with reference to all physicians residing therein. It is also expected that your committees will provide the information necessary to avoid the indiscriminate dislocation of practitioners who are in essential capacities.

Your chairman agreed to serve in the capacity suggested by Mr. McNutt and now found himself with the necessary committees below the state level in the districts already mentioned, and with plans for the formation

of such committees in all districts. It was left to organize the appropriate state committee.

Your chairman consulted with your president and, as a result, will propose to Mr. McNutt the following names for members of the state committee:

H. M. Clute, Suffolk  
J. J. Curley, Worcester North  
E. L. Kichham, Norfolk  
Dwight O'Hara, Middlesex South  
W. H. Pulsifer, Plymouth

On January 30, the first assignment of work commenced. A list of names was forwarded to your chairman from Washington, comprising a group of forty-five physicians under the age of thirty-six, who already have enrolled with Procurement and Assignment Service with a view to immediate commission in the Army or Navy. This list is to be scrutinized by the appropriate committees in the districts where the men live, to discover if for any reason any of these young doctors should be regarded as unavailable for immediate service.

The following table has been made to give a bird's-eye view of this initial list:

DISTRICT	NUMBER OF CANDIDATES	DISTRICT	NUMBER OF CANDIDATES
Barnstable	0	Middlesex East	0
Berkshire	1	Middlesex North	1
Bristol North	1	Middlesex South	6
Bristol South	1	Norfolk	6
Essex	3	Norfolk South	2
Essex North	1	Plymouth	0
Franklin	1	Suffolk	12
Hampden	4	Worcester	7
Hampshire	3	Worcester North	1

The candidates are widely scattered, suggesting the need for alert committees in each area and that there will be considerable work on the classification of physicians throughout the entire State.

It is gratifying to be able to report that returns from four districts already have been received because the Procurement and Assignment Service in Washington emphasizes the fact that reports on these candidates are required as quickly as possible. The spirit of these returns is praiseworthy in suggesting that the work of classifying doctors in Massachusetts will be done quickly and unselfishly. For example, one chairman reporting for his committee concerning a candidate wrote: "He is one of the most outstanding young surgeons in our community. I dislike very much to say he is available for military service, but in all fairness I cannot say anything else as our community most certainly can get along without him and he should be a great asset either to the Army or the Navy." This is a model of the way in which each doctor should be considered.

It is the work of your committee continues to develop as successfully in future as it has during the first few days of its active existence, its accomplishments should be a credit to the efforts of the Society toward being helpful to the country during the present emergency.

REGINALD FITZ, *Chairman*

## APPENDIX NO 16

### REPORT OF THE COMMITTEE ON REHABILITATION

This committee was formed by the president of the Massachusetts Medical Society at the last regular meeting of the Council, on October 1, 1941. It was formed largely, as we understand it for the purpose of assisting the Division on Health of the Massachusetts Committee on Public Safety, the chairman of which committee is Professor Curtis Hilliard. Several meetings have been attended by

one or more members of your committee in conjunction with Professor Hilliard.

On or about November 14, 1941, the secretary of the Massachusetts Medical Society attended a meeting in Chicago, at which various plans were discussed for rehabilitation of those who, because of various defects, had failed to pass selective-service medical examinations. We are informed that no definite program was adopted at that meeting.

On December 22, 1941, one of us met with Professor Hilliard and others of his committee. We learned on that date that the committee of the Massachusetts Dental Society unofficially endorsed the health program of the Massachusetts Committee on Public Safety. Official endorsement was expected at a meeting to be held later by the Executive Committee of the Dental Society.

The directors and the members of the State Health Executive Committee would appreciate very much a communication from the Council of the Massachusetts Medical Society, endorsing their general program and assuring them of our co-operation and support. Professor Hilliard's committee has done a great deal of work on this matter, and several hundred rehabilitation agents have been named throughout the State. In order to be sure in what way the members of the Massachusetts Medical Society might co-operate with Professor Hilliard and his committee, and in order to be reasonably clear as to the program on which he would be pleased to have our endorsement, we asked him to outline in writing his proposed work, and this he has done in a communication dated January 3, 1942, a copy of which follows:

We are enclosing a copy of the dental statement of the attitude and policy which the Committee on Rehabilitation of the Massachusetts Dental Society are submitting to their Council. While this statement is cautious, I feel that on the whole it can be considered that the dental profession will be sympathetic with our rehabilitation program and it will go along with us as our plans develop.

We would like your committee of the Massachusetts Medical Society to consider recommending to the State Council some expression of their endorsement of the rehabilitation program in general and of the willingness of the State Society to recommend to their membership the co-operation of the local societies and of individual physicians. We do not consider that the plan necessarily involves giving of free medical service or advice. Our rehabilitation agents who are, ordinarily, trained people, may have cases where some leniency in respect to fees and time of payment may be desirable. We would also like from your committee a statement regarding the relation of certain other professional groups to the rehabilitation work. For example, the Boston Society of Optometrists have offered, without stint, the services of their Boston Clinic in the work of rehabilitation and they are placing this matter before their State society. We believe that the ophthalmologists may likewise be drawn into our plan. More difficult is the handling of the chiropodist group who have already offered to help us. (I suppose that then we have just got to be practical but I would like the expression and opinion of your committee.)

These are the chief things that occur to me at the moment on which we would like to act but it may well be that your group will give us some useful advice or suggest some action that they can take which will be helpful to us. We appreciate greatly the time and thought you personally are giving this matter and also the willingness of your colleagues to co-operate.

Pursuant to receipt of this communication, Professor Hilliard was advised that unless time was of the essence, no action would be taken by the Massachusetts Medical Society until the Council meeting which would be held on February 4.

Those in authority who have had to do with the examination of selectees have compiled various groups of statistics. It has been necessary, we are told, to examine five selectees in order to obtain two fit for military service. A great many of those turned down are anxious to have remedial defects attended to. Professor Hilliard's committee is taking a long-range view as to what may be done generally to improve the health of the citizens of this commonwealth. Again, as we understand it, his committee has not for its prime object the rehabilitation of those who wish to be made fit so that they may enter service forthwith. However, at the regular monthly meeting of the Boston Hospital Council held in November, endorsement of Professor Hilliard's work was given with reference to those seeking medical aid in order that they may be admitted to the air forces of our country.

If the Council of the Massachusetts Medical Society to-day approves, the Committee on Rehabilitation will report in substance to Professor Hilliard as follows:

The members of the Massachusetts Medical Society are deeply appreciative of the work undertaken by the State Health Executive Committee of the Massachusetts Committee on Public Safety. Ever since the Massachusetts Medical Society held its first meeting in 1781, its members have felt privileged to be of assistance to those afflicted by disease or injury, or those handicapped because of various defects. We are well aware that many others, not members of the Massachusetts Medical Society, have, so far as their ability permitted, been interested in no small way in measures which have had to do with the health and well-being of our citizens. We are not well enough acquainted with the work and programs undertaken by professional groups who are not physicians but who are interested in the health of our citizens so that we might give blanket approval of their respective programs. The members of the Massachusetts Medical Society are keenly aware of the tremendous amounts of money now being expended in the defense of our country. We believe no programs now in force have effected any change in the status which has long continued to exist and which exists at the present time between physicians and patients in this commonwealth. We do expect reasonable financial remuneration from those who are able to pay for our services as they may be required in this program of rehabilitation. However, not in the past and certainly not now will any members of the Massachusetts Medical Society permit any individual who needs medical or surgical care or advice relative to matters of health to go without these services because the individual is unable to pay for same. From time to time as the Executive Health Committee on Public Safety wishes assistance from the members of the Massachusetts Medical Society, we would appreciate hearing from the Executive Health Committee or from any of the numerous rehabilitation agents throughout the State, and with them we shall endeavor to co-operate so far as we may reasonably and properly do so in this matter of rehabilitation.

WILLIAM M. COLLINS  
DAVID C. DOW  
JAMES J. REGAN  
BENJAMIN F. ANDREWS  
WILLIAM E. BROWNE, *Chairman*

# MEDICAL PROGRESS

## ENDOSCOPY\*

EDWARD B. BENEDICT, M.D.†

BOSTON

**A**LTHOUGH endoscopic procedures are naturally best carried out by specialists, the general practitioner is frequently called on to decide whether or not such examinations are indicated. It is for this reason that physicians in general practice must be interested in endoscopic progress, for it is only through the co-operation of all physicians that such examinations are performed on the right patients at the right time.

### ANESTHESIA

Anesthesia for peroral endoscopy has been reviewed by Jackson and McReynolds,<sup>1</sup> who believe that cocaine is the most efficacious drug for local anesthesia, and that if it is used with care, serious reactions will be rare. They believe that Pontocaine is fairly satisfactory but is contraindicated in asthma patients. Larocaine in their experience has been absolutely nontoxic but has also been less effective. General anesthesia is used in the Jackson Clinic very rarely. In my opinion, almost all endoscopic procedures can and should be done under local anesthesia. For some time, all peroral endoscopies in the clinic at the Massachusetts General Hospital have been done under 5 per cent Larocaine, which appears to be sufficiently efficacious and is less toxic than cocaine or Pontocaine. All peritoneoscopies are done with 1 per cent novocain.

### BRONCHOSCOPY

#### *Bronchial Anatomy*

Adams and Davenport,<sup>2</sup> in a very careful study on the technic of bronchography and a system of bronchial nomenclature, have attempted to standardize the various divisions and segments of the five major lobes of the lung. They propose a simplified terminology based on careful anatomic studies that will meet the practical needs of internists, radiologists, bronchologists and surgeons. The use of a common language in describing the tracheobronchial tree will do much toward a correct interpretation of clinical, roentgenologic and bronchologic findings.

\*Reprints of articles in this series are not available for distribution but the articles will be published in book form. The current volume is *Medical Progress Annual, 1940* (Springfield, Illinois: Charles C. Thomas Company, 1941, \$4.00).

†From the Massachusetts General Hospital.

Assistant in surgery, Harvard Medical School, associate visiting surgeon, Massachusetts General Hospital.

#### *Use in Various Diseases*

**Bronchiectasis.** Schenck,<sup>3</sup> in a discussion on the etiology of bronchiectasis, observes that the high incidence of sinus disease is not accidental and that therapy of chronic suppurative disease of the lower respiratory tract is doomed to failure if it does not include the thorough treatment of sinus infection. I agree that careful treatment of sinus disease is essential in the care of bronchiectatic patients.

In a recent symposium, it was emphasized that bronchiectasis is frequently a sequela or complication of the pulmonary phase of an acute infectious disease of childhood. In discussing the prevention of bronchiectasis, Tucker<sup>4</sup> states that the expulsive effort of the cough mechanism is much feeble in infants and young children than in adolescents and adults. The retention of the obstructive secretions is favored by this feebleness of effort, and when the effort is obtunded or suppressed entirely by the toxicity of the general infection or by the administration of sedatives, a condition results that is ideal for, and in many cases is undoubtedly the cause of, atelectasis and bronchiectasis in young children. On this basis, Tucker advocates bronchoscopic treatment of children with these conditions and considers the results of aspiration and drainage in such patients remarkable.

Tucker<sup>5</sup> has recently pointed out the value of chemotherapy in the treatment of bronchiectasis. By means of an endobronchial insufflator, he has introduced sulfadiazine into the major bronchi at the time of bronchoscopic aspiration. This form of therapy is well tolerated, produces no bronchial obstruction, and in some cases has resulted in striking improvement. A constant blood level can be maintained. Sulfanilamide may be used, but sulfadiazine is probably better. According to Churchill,<sup>6</sup> peroral chemotherapy may be beneficial in bronchiectasis, but I believe that intrabronchial administration, with aspiration of bronchial secretions at regular intervals, will be of greater benefit. Holinger, Basch and Poncher<sup>7</sup> have made a valuable study on the influence of expectorants and gases on sputum and the mucous membranes of the tracheobronchial tree. They emphasize the fact that drainage of pathologic secretions in the

bronchi depends to a large degree on liquefaction of these secretions by the action of the glands of the more normal bronchial mucosa; by an increase in liquefaction, expectoration is aided. Following the administration of carbon dioxide, patients with low-grade bronchiectasis were found to have less secretion in their bronchi. The secretion was also of a constantly lower viscosity than that noted when carbon dioxide was not used. Carbon dioxide is therefore considered an extremely efficient expectorant. Oxygen, moreover, was found to be definitely antiexpectorant. In bronchiectasis and in certain types of asthma in which bronchial obstruction plays a role, frequent inhalations of carbon dioxide by mask, together with steam inhalations, may be used to augment postural drainage and bronchoscopic aspirations, which are fundamentally important. The use of steam and carbon dioxide between bronchoscopies is indicated if the sputum is known to be extremely thick and tenacious. In laryngotracheobronchitis, the use of a room kept at 70 to 75°F., together with a relative humidity of 80 to 95 per cent, provides satisfactory conditions for liquefying secretions. If oxygen administration is necessary, a high degree of humidity in the oxygen tent is essential. A combination of steam inhalation and carbon dioxide has been found to be the most efficient expectorant in the treatment of postoperative massive collapse. When these methods fail, bronchoscopic suction must be used. Carpenter, Kerr and McMurray,<sup>8</sup> who have treated a group of 38 cases of bronchiectasis by x-ray therapy, conclude that such therapy is only moderately satisfactory. They do believe, however, that it may be a valuable adjunct in the treatment of patients whose pulmonary lesions are not amenable to surgery and whose symptoms have not been relieved by other forms of treatment, such as bronchoscopic and postural drainage.

Bradshaw, Putney and Clerf<sup>9</sup> made a follow-up study of 242 cases of untreated bronchiectasis. They report that the average duration of life from the onset of symptoms to the time of death was over thirteen years. They believe that young children with definite evidence of bronchiectasis may later show no evidence of the disease—lack of symptoms and negative studies with iodized oil; in other words, bronchiectasis in early childhood may sometimes be cured by proper bronchial drainage.

*Postoperative pulmonary complications.* The use of the bronchoscope in the postoperative aspiration of secretions is becoming more widely recognized by general surgeons. Allen<sup>10</sup> believes that bronchoscopy for this purpose is so vital that all

anesthetists should be trained in its technic. Such training is now being carried out at the Massachusetts General Hospital.

*Lung abscess.* Moersch and Olsen<sup>11</sup> report on the value of bronchoscopy in the diagnosis and treatment of pulmonary abscess: the procedure established the exact location of the abscess in 22 out of 264 cases. They report very good results from the bronchoscopic treatment of lung abscess. I consider this a debatable subject, however, since some cases of lung abscess are cured under medical treatment and others under a combination of medical and bronchoscopic treatment, whereas many require surgical drainage and a few are best treated by lobectomy. Lung abscess, therefore, like many other pulmonary conditions, is best handled by the internist, thoracic surgeon, bronchoscopist and roentgenologist, all working together.

*Carcinoma.* Betts<sup>12</sup> divides pulmonary carcinoma into central and peripheral groups, depending on the site of origin of the lesion. He regards the central group as more favorable from a therapeutic standpoint because such lesions produce symptoms earlier than the ones distally situated; because they can be visualized and biopsied bronchoscopically, which permits an early positive diagnosis; and because there is evidence<sup>13</sup> that tumors in the central location grow more slowly and metastasize later than lesions situated peripherally. In peripherally located tumors, aspiration biopsy is sometimes of use, although, as Franseen<sup>14</sup> points out, there is some risk of implantation in the chest wall and pleural cavity.

*Benign tumors.* Goldman and Stephens<sup>15</sup> call attention to the fact that pulmonary resection appears to be the ultimate fate awaiting most patients with bronchial adenoma. This is so not only because of the persistence of the tumor itself but also because of the presence of distal pulmonary suppuration. I agree with this and, in fact, have recently pointed out that only a few cases of bronchial adenoma are completely cured anatomically as well as clinically by the bronchoscopic method.<sup>16</sup> The failure to obtain complete cure by bronchoscopy alone is due to the occurrence of irreparable lung damage distal to the tumor, to the recurrence locally of the adenoma and to the extrabronchial growth of the lesion. Bronchoscopy, however, is of great value in the diagnosis of adenoma, and in some cases, bronchoscopic removal results in almost complete relief of symptoms.

*Tuberculosis.* Davenport<sup>17</sup> has studied 10 cases of tuberculous tracheobronchitis with special reference to x-ray therapy, which he believes to be of benefit in the acute obstructive stage of the dis-

er. In occasional cases, Benedict<sup>18</sup> has noted unquestionable benefit from dilatation of a tuberculous stricture, with the consequent release of retained secretions.

## ESOPHAGOSCOPY

### *Use in Various Diseases*

*Carcinoma* Garlock<sup>19</sup> believes that cancer of the esophagus is usually a slow-growing neoplasm and that the next few years will see the acceptance of surgical treatment as the only sound therapy. More rapid progress in the surgical treatment will be made when increasing numbers of early cases (patients with persistent dysphagia) in which esophagoscopy, biopsy, fluoroscopic and roentgenographic examinations have been done are referred to the surgeon. In a recent discussion on the surgical treatment of carcinoma of the esophagus, Adams<sup>20</sup> remarks that the frequency of this disease has only recently become appreciated. He finds that it ranks fourth in incidence of all malignant tumors in men over twenty years of age. Successful operative management depends almost entirely on early diagnosis, and early diagnosis, in turn, depends on the education of the profession as a whole to the awareness of the gravity of dysphagia and the value of immediate x-ray and esophagoscopic examinations. In a discussion on carcinoma of the esophagus from the point of view of the endoscopist, Benedict<sup>21</sup> has emphasized the fact that by early diagnosis an increasingly large proportion of the patients with carcinoma of the esophagus may be cured by radical surgery. Churchill<sup>22</sup> and Sweet<sup>23</sup> have demonstrated the great value of the transthoracic approach in surgery of the lower esophagus and upper stomach. When, however, patients are seen too late in the disease for surgery, much can be accomplished in the way of palliation by x-ray treatment combined, if necessary, with bouginage. Gastrostomy is seldom necessary.

*Benign stricture* Hara and Rosenfold,<sup>24</sup> in a discussion of cicatricial atresia of the esophagus, call attention to the advantage of using a cystoscope for retrograde esophagoscopy, since it reveals a wider area and gives a better view of the field than can be obtained through an open tube esophagoscope. The cystoscope is introduced through a gastrostomy wound and insinuated into the esophagus under visual guidance. A ureteral catheter may then be introduced upward through the stricture, with fluoroscopic guidance, if necessary.

*Cardiospasm* Ochsner and DeBakey<sup>25</sup> have recently discussed the surgical treatment of achalasia

of the esophagus, believing the soundest surgical procedure to be esophagogastrostomy, the technic of which is illustrated. They find that slightly less than one third of the cases require surgical intervention. It is my opinion, however, that more than 90 per cent of these cases can be satisfactorily treated by conservative measures.

*Varices* Moersch<sup>26</sup> has made a further report on the treatment of esophageal varices by injection of sclerosing solutions. He is now using 5 per cent sodium morrhuate and giving injections of 5 to 7 cc twice a week. In a series of 11 patients, four hemorrhages occurred subsequent to treatment. Further experience will be necessary before the method can be finally evaluated, but there is some evidence that the hemorrhages are less frequent and less severe.

*Syphilis* Kampmeier and Jones<sup>27</sup> have reported 4 cases of esophageal obstruction due to syphilis, 1 was the result of a gumma of the esophageal wall, and 3 were caused by gummatous lesions of the diaphragm at the esophageal hiatus. The symptoms are those of esophageal obstruction. The diagnosis is made by serologic and roentgenologic examinations, in addition to esophagoscopy and biopsy. Three of the 4 patients were cured by antisyphilitic treatment and dilatation of the esophageal strictures. One case was diagnosed as carcinoma of the esophagus, and the patient died without receiving appropriate treatment.

### *Relation of Nutritional Deficiency to Dysphagia*

Merrill and Richards<sup>28</sup> have re-emphasized the significance of nutritional deficiency and its relation to dysphagia, concluding that difficulty in swallowing is occasionally a result of neuritis involving the ninth or tenth cranial nerve, which in turn is produced by nutritional deficiency, particularly of the vitamin B complex.

### *Influence of Psychic Factors on Esophageal Tone*

Faulkner,<sup>29</sup> in an esophagoscopic study of 13 cases, has observed esophageal changes due to psychic factors. During inspection of the esophagus, he has shown that disturbing thoughts and emotions produce esophageal spasm. This spasm can be increased and the esophageal lumen narrowed or closed by suggestions that call forth destructive emotions, such as grief, anger, anxiety, apprehension, fear and spiritual imprisonment. The esophageal spasm relaxes when proposals are made eliciting such emotions as happiness, elation, enthusiasm, contentment and security. I believe that this is a difficult matter to prove, since respiratory, circulatory, traumatic and other factors come into the picture.

## GASTROSCOPY

*Indications*

Since it is imperative for physicians to know when special procedures should be used, Benedict<sup>30</sup> has listed the indications for gastroscopy as follows: gastritis; unexplained gastrointestinal hemorrhage; so-called "gastric neurosis"; unexplained persistent gastrointestinal symptoms, with negative or inconclusive x-ray examination; gastric ulcer, to determine the appearance and location of the lesion, to differentiate benign from malignant ulcer, and to follow the healing process in benign ulcer; duodenal ulcer, to study the gastric mucosa for the presence of gastritis, gastric erosions or gastric ulcerations; carcinoma, to determine the gross appearance, extent and operability of the lesion; polyposis; the so-called "postoperative stomach"; and occasional cases of suspected foreign body in the stomach.

*Gastroscopy in the Armed Forces*

Schindler,<sup>31</sup> who has recently discussed the advantage of the gastroscope in the diagnosis of gastric diseases in soldiers, concludes that the differential diagnosis of psychoneurosis and chronic gastritis in patients suffering from epigastric distress is of great consequence to all branches of the armed forces. The cases presented prove that this differential diagnosis is possible only by the use of the gastroscope. Most patients who refuse examination and fail to co-operate are malingerers. Facility for gastroscopy should be available to all military hospitals.

*Gastroscopic Method*

To determine the safety of gastroscopy, Schindler<sup>32, 33</sup> sent out a questionnaire and received replies from sixty gastroscopists, who reported their experiences during 22,351 gastroscopies. In this series, there was one death that must probably be attributed to the use of the gastroscope. Thus, the fatality of gastroscopy is 0.004 per cent, or practically nil.

Kenamore<sup>34</sup> has reported the invention of a biopsy forceps to be attached to the flexible gastroscope. He claims that the instrument can be employed effectively in any portion of the stomach that is visible gastroscopically. I believe that this may be an important advance in gastroscopic technique in carefully selected cases.

*Use in Various Diseases*

*Alcoholic gastritis.* Gray and Schindler<sup>35</sup> have recently reported the gastroscopic appearance of the gastric mucosa of chronic alcoholic addicts. Examination of 100 men who had consumed an average of 2.8 pints of distilled liquors daily for

more than twenty years revealed that the stomachs of 55 per cent were essentially normal. The gastric disease observed in 45 per cent consisted mainly of superficial gastritis, atrophic gastritis or a combination of the two. Mucosal hemorrhages occurred in 22 per cent. Severe or moderately severe gastritis was accompanied by definite symptoms in 60 per cent, whereas only 7 per cent of the addicts with normal stomachs had gastrointestinal complaints. No correlation was observed between the incidence and severity of the gastritis and the duration of the alcoholism, the amount of alcohol drunk, the abuse of nicotine, dental infection or vitamin deficiency. The cause of the gastritis observed in 45 per cent of the cases was not clear, but might be ascribed to an individual sensitivity to alcohol or to a deficiency disease, although apparently not specifically to a vitamin deficiency. These observations are borne out by Berry,<sup>36</sup> who also studied 100 patients with unquestionable chronic alcoholism of long duration and found that 30 per cent did not have gastritis, 35 per cent had mild chronic superficial gastritis and only 35 per cent had unequivocal chronic gastritis.

*Chronic gastritis.* McClure, Sweetsir and Janekelson,<sup>37</sup> in a gastroscopic and clinical study of chronic gastritis, have emphasized the significance of hematemesis as a complication of this disease. They also believe that fatigue is a major symptom characterizing primary atrophic gastritis. The presence of chronic gastritis can apparently be demonstrated only by means of gastroscopy.

Kelley, Lawlah and Berry<sup>38</sup> studied the gastric mucosa by the x-ray relief technic and correlated their findings with the gastroscopic diagnosis in 150 cases of benign and malignant gastric neoplasm, ulcer and chronic gastritis. They conclude that the relief method demonstrates these lesions accurately except in chronic gastritis, and that if one attempts a diagnosis of chronic gastritis by x-ray it should be done with great reservation.

*Atrophic gastritis.* In discussing the treatment of atrophic gastritis, Schiff and Goodman<sup>39</sup> present the case histories of 5 patients treated by desiccated hog's stomach extract (Ventriculin), with marked symptomatic improvement and disappearance of the atrophic changes. These results suggest that atrophic gastritis, perhaps better called "gastric atrophy," in some cases may be a deficiency disease. This is further corroboration of the evidence originally presented by Jones, Benedict and Hampton,<sup>40</sup> who showed that in pernicious anemia the changes characterizing gastric atrophy may disappear following liver therapy.

**Post-operative gastritis.** Moersch and Walters<sup>41</sup> have made gastroscopic observations in cases of gastric distress following operations on the stomach and conclude that, contrary to the commonly accepted teaching that gastritis is found in all stomachs after operation, 30 per cent of this series of cases failed to show gastroscopic evidence of disease. Evidence of gastritis was present, however, in 56 per cent of the cases studied. In speculating on the possible factors in postoperative gastritis, the writers believe that in many cases a pre-existing gastritis is responsible. In their opinion, a poorly placed stoma with inadequate drainage of the stomach is a major factor, in addition, if the stoma retains an activity resembling that of a sphincter, gastritis is not so likely to develop. Infection undoubtedly constitutes an important exciting factor.

**Ulcer.** Walters and Clagett<sup>42</sup> discuss the value of gastroscopy in the diagnosis of gastric ulcer, pointing out that although the accuracy of roentgenologic diagnosis of lesions of the stomach is remarkably high, there is always the chance that a small lesion or one situated high in the stomach may be overlooked. Gastroscopy should always be considered in a patient in whom there is a suggestion of a gastric lesion, even though the roentgenologic examination does not reveal any abnormality. Gastroscopy is of considerable value in distinguishing between a benign gastric ulcer and a malignant ulcer and may offer valuable information concerning the operability of the lesion. Gastroscopy is also a great aid in determining the effect of medical management on gastric ulcers. The authors do not consider gastroscopy necessarily a routine procedure in all gastric examinations but have found it to be a valuable adjunct to clinical and roentgenologic study of selected cases of known or suspected gastric disease.

Eusterman,<sup>43</sup> in a paper on carcinomatous gastric ulcer states that the most reliable evidence regarding the extent of healing of a gastric lesion is undoubtedly afforded by gastroscopic examination. When physicians and surgeons who do not do gastroscopy themselves make such statements, one may conclude that the value of the gastroscopic method is now becoming widely recognized.

**Carcinoma.** In several exhaustive studies of carcinoma of the stomach, Schindler<sup>44</sup> has emphasized the status of chronic gastric atrophy as a precancerous condition. He believes that this is a frequent disease, and that an accurate diagnosis is made only by gastroscopy. Clinically, these patients may have long periods of freedom from symptoms, but they usually complain of minor

epigastric distress, pressure, belching or pain. The general symptoms of extreme fatigue, nervousness, numbness and tingling of the limbs are most characteristic. Schindler observes that patients with gastric atrophy or atrophic gastritis are three times likelier to develop gastric carcinoma than other healthy adults. The advantage of frequent x-ray and gastroscopic examinations in such patients is therefore obvious. With regard to the classification of gastric carcinoma, Schindler and his associates<sup>45</sup> have noted that the ultimate prognosis of patients suffering from gastric carcinoma does not depend on the size of the tumor or, apparently, on the microscopic structure of the tumor. They therefore suggest the adoption of Borrmann's classification, based on the gross appearance. In this grouping, Type 1 is the polypoid carcinoma characterized by a broad base supporting a hemispherical elevation, which is solid and whose surface consists of numerous nodes of different sizes; the edge of the growth is sharply limited, and it is often overhanging in a mushroom-like manner. This type is found in 2.9 per cent of all cases. Type 2, the noninfiltrating, carcinomatous ulcer, consists of a lesion that is usually rather large. Its color, as seen in the gastroscope, is a dirty gray or a brilliant white, brownish, purplish and reddish hues being frequently present; this ulcer is surrounded by a thick, high, usually nodular wall, which is limited sharply toward the surrounding gastric mucosa and slopes steeply toward it. This type has been found in 17.6 per cent of all cases. Type 3, the infiltrative carcinomatous ulcer, comprises a lesion that lies in the center of a marked elevation. At one side of it, a wall may be found that is either smooth or, more frequently, nodular; there is a gradual infiltration into the surrounding mucosa, and the wall never surrounds the entire ulcer. Type 3 carcinomas occur in 16.3 per cent of all cases. Type 4 is the diffuse infiltrating type, with no sharp limitations. Shallow or deep ulcerations are frequent, and gastroscopic as well as x-ray examination teaches that such ulcers may heal for some time, other ulcers developing at other places of the carcinomatous infiltration. This type occurs in 63.2 per cent of all cases. Schindler et al conclude that classification of gastric carcinoma, with consideration of its ultimate prognosis, should be attempted and that histologic criteria according to the usual conceptions, especially grading, seem not to have a relation to the gross appearance of gastric carcinoma, to its clinical course or to its surgical curability. Therefore, new attempts should be made to find histologic criteria in better accord-



ance with those factors. Gross classification has proved to be satisfactory. The preliminary impression is gained that excellent results after surgical interference are to be expected with the non-infiltrating lesions (Types 1 and 2), whereas the prognosis with infiltrating lesions (Types 3 and 4) is unfavorable. Needless to say, this requires confirmation by extensive research. In my opinion, the findings are significant, and extensive gastroscopic observations regarding gross typing of tumors should be made. It should be borne in mind, however, that the gross typing is not always a simple matter.

### PERITONEOSCOPY

#### *Method*

In a preliminary report, Robinson and Fiske<sup>46</sup> describe an instrument for retraction of the viscera during peritoneoscopy. In selected cases, this may lead to a widening of the usefulness of the procedure.

#### *Evaluation*

Garrey<sup>47</sup> states that in 25 per cent of the cases he has examined by peritoneoscopy, the findings fundamentally altered the treatment. In the remainder, accurate confirmation of a suspected diagnosis was obtained. He concludes that the procedure is essential to the study of abdominal tumors and liver disease, if needless laparotomies are to be avoided. He emphasizes the fact that it involves only a fraction of the expense or mortality of a major operation. Benedict<sup>48</sup> in an analysis of 300 peritoneoscopies, concludes that it is a safe, simple and accurate method of diagnosis by direct inspection of the abdominal cavity, including the pelvis, and that it will frequently lead to a positive diagnosis not obtainable by any other method except exploratory laparotomy. A positive biopsy was obtained in 100 cases as follows: carcinoma 70, cirrhosis 21, tuberculosis 4, hepatitis 2, sarcoid 1, sarcoma 1 and granuloma 1. Unnecessary exploratory laparotomy was avoided in 37 per cent of the cases.

In a discussion on the value of peritoneoscopy in gastroenterology, Benedict<sup>49</sup> has emphasized the advantage of this procedure in carcinoma of the stomach to avert operation in inoperable cases. It is also indicated occasionally in carcinoma of the colon, rectum, pancreas, liver and gall bladder, especially to differentiate cirrhosis and neoplasm. Also of interest to the gastroenterologist is its use in tuberculous peritonitis and in the

differentiation of ascites due to pelvic disease and that due to cirrhosis.

#### *Use in Various Diseases*

*Primary carcinoma of the liver.* One of the principal uses of peritoneoscopy is in the diagnosis of liver disease, especially carcinoma. Although metastatic carcinoma is far commoner than primary carcinoma of the liver, the latter occurs with sufficient frequency to be of interest. It almost always occurs secondarily to a pre-existing cirrhosis. Although rare in Europeans, Berman<sup>50</sup> reports that it is very common among most pigmented races. In the Bantu races of South Africa, he states that it is by far the most frequent type of carcinoma, since it is responsible for 90.5 per cent of all cancers. Metastasis is frequent. Thirty-one of 54 cases (57 per cent) showed secondary deposits outside the liver. Of all organs, the lungs were the most readily involved; there were 21 cases of lung involvement, in 25 of which both lungs were affected. Next most frequently involved were the regional lymph nodes (8 cases). Other organs affected were the pancreas, diaphragm, omentum, gall bladder, mesentery, peritoneum, pleura, heart, ribs, sternum and brain.

*Carcinoma of the ovary.* In an article on carcinoma of the ovary, Meigs<sup>51</sup> states that there can be no doubt of the value of peritoneoscopy in this group of patients and that it must be used more frequently in diagnosing these tumors. In my opinion, this is a well-established fact. In many cases of unexplained ascites, ovarian tumors with peritoneal metastases have been demonstrated by the use of the peritoneoscope. In a few cases in which radical mastectomy had been performed for carcinoma of the breast, ascites later developed and was thought to be due to metastatic disease from the breast. Peritoneoscopy, however, disclosed a primary malignant lesion in the ovary, with peritoneal metastases. X-ray therapy, with or without oophorectomy, was then carried out.

*Cirrhosis.* Mann<sup>52</sup> has repeatedly emphasized the fact that liver function may be impaired in one respect but not in others. Paulson<sup>53</sup> has also stated that the multiple functions of the liver require the use of multiple tests. Mateer, Baltz, Marion and Hollands<sup>54</sup> stress the advantage of performing several hepatic-function tests in an adequate evaluation of the liver function. The significance of recognizing acute hepatitis has been shown by Krarup and Roholm,<sup>55</sup> who by means of aspiration biopsy demonstrated a gradual transition in 12 cases of grave protracted or recurring hepatitis—from the usual acute hepatitis to fully developed Laennec's cirrhosis. None of

the patients in question were addicted to alcohol. Bearing in mind the inadequacy of liver function tests, I believe that during observations of the liver with the peritoneoscope, peritoneoscopic biopsy is superior to aspiration biopsy and will assume an increasingly important role in hepatic diagnosis.

## REFERENCES

- 1 Jackson C L and McPeaynolds G S Anesthesia for peroral endoscopy. *Transactions of the American Bronchoesophagological Association* New York City June 1940. Pp 68-78.
- 2 Adams R and Davenport I F The technique of bronchography and a system of bronchial nomenclature. *J Am J 118* 111-116 1942.
- 3 Schneck H P Etiology of bronchiectasis. *Arch Otolaryng* 34:95 95 1941.
- 4 Tucker G Bronchoscopic aspects of bronchiectasis. *Arch Otolaryng* 34:999 1013 1941.
- 5 Idem Presidential address. *Ann Otol Rhin & Laryng* (in press).
- 6 Church H E D Personal communication.
- 7 Holliger P, Hatch F P and Poncher H G The influence of expectorants and bases on sputum and the mucous membranes of the tracheobronchial tree. *J Am J 117* 675-678 1941.
- 8 Carpenter R C, Kerr H D and McMurray J S Roentgen therapy for bronchiectasis. *Arch Otolaryng* 34:913-919 1941.
- 9 Bradshaw H H, Putney F J and Clerf L H The fate of patients with untreated bronchiectasis. *J Am J 116* 2561-2563 1941.
- 10 Allen A W Abdominal surgery. *New Eng J Med* 226:57-63 1942.
- 11 Merck H J and Olsen A M Role of bronchoscopy in the treatment of pulmonary abscess. *Surgery* 9:905-915 1941.
- 12 Bell R H Carcinoma of the lung bronchoscopic aspects. *New Eng J Med* 225:519-525 1941.
- 13 Tuttle W M and Womack N A Bronchogenic carcinoma: a classification in relation to treatment and prognosis. *J Thoracic Surg* 4:125-146 1934.
- 14 Franzen C C Aspiration biopsy with a description of a new type of needle. *New Eng J Med* 224:1054-1058 1941.
- 15 Goldman A and Stephens H B Polypoid bronchial tumors with special reference to bronchial adenomas. *J Thoracic Surg* 10:327-333 1941.
- 16 Benedict F B Discussion of Jackson C L and Kornelmann F W So-called adenoma of the bronchus. *Ann Otol Rhin & Laryng* 50:1264-1264 1941.
- 17 Davenport I F Tuberculous tracheobronchitis: radation therapy. *Am J Roentgenol* 45:494-504 1941.
- 18 Benedict F B Bronchoscopic dilatation of bronchial stenosis following thoracoplasty for tuberculosis. *New Eng J Med* 220:617-620 1939.
- 19 Garlock J H Problem of cancer of esophagus. *J Mt Sinai Hosp* 7:349-352 1941.
- 20 Adams W F The pathological considerations relating to the early diagnosis and curative surgical treatment of carcinoma of the esophagus. *Internat Abstr Surg* 72:105-110 1941.
- 21 Benedict F B Carcinoma of the esophagus with special reference to treatment by radical surgery x-ray and bougienage. *Ann Otol Rhin & Laryng* 50:1249-1263 1941.
- 22 Church H E D Personal communication.
- 23 Sweet R H Transhiaphragmatic partial gastrectomy for carcinoma high in the stomach. *Rev Gastroenterol* (in press).
- 24 Hira H J and Rosenwald L K Cicatricial atresia of the esophagus. *Arch Otolaryng* 34:574-582 1941.
- 25 Ohmer A and Delbak M The surgical treatment of achalasia of the esophagus. *Surg Gynec & Obst* 72:290-297 1941.
- 26 Moersch H J Treatment of esophageal varices by injection of sclerosing solution. *J Thoracic Surg* 10:300-309 1941.
- 27 Kampmeier R H, and Jones C Esophageal obstruction due to gummas of esophagus and diaphragm. *Am J M Sc* 201:539-546 1941.
- 28 Merrill D and Richards E Dysphagia and nutritional deficiency. *New Eng J Med* 225:326-330 1941.
- 29 Fulkner W B Jr Objective esophageal changes due to psychic factors: an esophagoscopy study with report of thirteen cases. *Am J M Sc* 200:796-803 1940.
- 30 Benedict F B Indications for gastroscopy. *New Eng J Med* 223:925-933 1940.
- 31 Schindler R On the importance of the gastroscope in the diagnosis of gastric diseases in the army. *Brit M J* 1:243-247 1940.
- 32 Idem Questionnaire on fatalities due to gastroscopy. *Am J Digest Dis* 6:557 1939.
- 33 Idem Results of the questionnaire on fatalities in gastroscopy. *Am J Digest Dis* 7:793-795 1940.
- 34 Kenmore D A biopsy forceps for the flexible gastroscope. *Am J Digest Dis* 7:539 1940.
- 35 Gray S and Schindler R The gastric mucosa of chronic alcoholic addicts. *J Am J 117* 1005-1011 1941.
- 36 Berry L H Chronic alcoholic gastritis: evaluation on the concept with gastroscopy studies in one hundred cases. *J Am J 117* 2233-2238 1941.
- 37 McClure C W, Sweetser F N and Jankelson I R Chronic gastritis: a gastroscopic and clinical study. *New Eng J Med* 225:259-263 1941.
- 38 Kelley C H, Lwlah J W and Berry L H Mucosal relief technique correlated with gastroscopy in one hundred and fifty cases. *Radiology* 36:77-85 1941.
- 39 Schiff J and Goodman S Desiccated hog's stomach extract (Venusal) in the treatment of atrophic gastritis. *Am J Digest Dis* 7:14-17 1940.
- 40 Jones C M, Benedict F B and Himpton A O Variations in the gastric mucosa in pernicious anemia: gastroscopic surgical and roentgenologic observations. *Am J M Sc* 190:596-610 1935.
- 41 Moersch H J and Walters W Gastroscopic observation in cases of gastric distress following operations on the stomach. *Surg Gynec & Obst* 71:129-134 1940.
- 42 Walters W and Cliggett O T The surgical treatment of chronic gastric ulcer: review of two hundred and seventy-two cases. *Surg Gynec & Obst* 71:75-79 1940.
- 43 Tusterman G B Carcinomatous gastric ulcer: misleading results of medical therapy. *J Am J 118* 15 1942.
- 44 Schindler R Early diagnosis of cancer of the stomach: gastroscopy and gastric biopsies, gastrophotography and x-rays. *J Nat Cancer Inst* 1:451-480 1941. Early diagnosis and prognosis of gastric carcinoma. *J Am J 115* 1093-1099 1940.
- 45 Schindler R, Steiner P E, Smith W M and Driley M E The classification of gastric carcinoma. *Surg Gynec & Obst* 73:30-39 1941.
- 46 Robinson S and Fiske L G An instrument for retraction of viscera during peritoneoscopy. *West J Surg* 49:284-293 1941.
- 47 Greer W E An evaluation of peritoneoscopy with particular reference to the diagnosis of abdominal tumors. *New Eng J Med* 225:180-184 1941.
- 48 Benedict F B Peritoneoscopy. *Oxford Medicine* (in press).
- 49 Idem The value of peritoneoscopy in gastroenterology: a review of one hundred cases. *Am J Digest Dis* 6:512-519 1939.
- 50 Berman C The pathology of primary carcinoma of the liver in the Bantu races of South Africa. *South African J M Sc* 6:11-26 1941.
- 51 Meigs J V Cancer of the ovary. *Surg Gynec & Obst* 71:44-53 1940.
- 52 Mann F C The liver and medical progress. *J Am J 117* 15-7 1932 1941.
- 53 Pailson M Practical application of liver function tests. *M Clin North America* 25:593-599 1941.
- 54 Mincer J G, Baltz J I, Marion D F and Hollands R A A comparative evaluation on of the newer liver function tests. *Am J Digest Dis* 9:13-29 1942.
- 55 Krarup N B and Roholm K Development of cirrhosis of liver after acute hepatitis illuminated by aspiration biopsy. *Nord med (Hospitaltidn)* 10:191-202 1941.

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTE-MORTEM AND POST-MORTEM RECORDS AS USED  
IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

### CASE 28111

#### PRESENTATION OF CASE

A sixty-five-year-old housewife was admitted to the hospital because of pain in the chest.

The patient was quite well until about an hour before entry, when, while talking to a friend, she suddenly became unconscious. After about an hour, when consciousness was regained, she complained of pain in the chest, described as a sense of suffocation and pressure between the scapulas, extending to the arms, the anterior and posterior parts of the neck and to the ears. She also complained of headache. There was some gagging, but no vomiting occurred. A physician found the patient to be pulseless, but restless, with active reflexes. There was no stiffness of the neck, the tongue was straight, and pupils were equal, with normal reactions. Morphine was given and the patient was referred to the hospital.

A brother of the patient died of tuberculosis at the age of thirty. During childhood, the patient had pleurisy. At the age of nineteen, she had typhoid fever. During convalescence from this illness, she had great difficulty in swallowing. At thirty-five years, after the birth of her second child, she was again unable to swallow for sixteen days. A year later, a physician found an esophageal stricture, which was then treated by dilatation. After that, the patient had to grind up all her food. When fifty-seven years old, she consulted a physician because of a mass in her neck consistent with an enlarged thyroid gland. The facies suggested myxedema. The heart and lungs were normal. The blood pressure was 115 systolic, 90 diastolic. The basal metabolic rate was -2 per cent. Small doses of thyroid were given, with some decrease in the size of the goiter. Two years later, after a nervous upset, the patient fainted in the street. She felt weak for four or five hours subsequently, but had no other ill effects; the blood pressure was 115 systolic, 85 diastolic. The thyroid gland felt cystic. A slight systolic murmur was heard all over the chest when the patient was supine. A year later, there was another attack of fainting. Two years later, the patient had bronchopneumonia, during which there was a paroxysm of auricular fibrillation.

The blood pressure was 160 systolic, 105 diastolic, but several months later returned to 104 systolic, 72 diastolic.

On admission, the patient was restless, quite talkative and slightly euphoric, although obviously very ill. The skin was ashen. The hands and feet were cold, but dry. The carotid pulse was weak, and no pulsations could be obtained in the extremities. The heart sounds were of good quality and fairly regular, although there were frequent premature beats. A blowing systolic murmur, loudest at the base, was transmitted to the neck and was also very loud over the back. There was no friction rub. The area of cardiac dullness was of normal size. The breath sounds were tubular posteriorly, but there were no rales or areas of dullness in the lung fields. The abdomen was rather rigid, but not tender. The liver and spleen were not palpable. Peristaltic sounds were distant. The veins of the neck were not distended, but the veins over the abdomen formed a distinct caput medusae. The neck was flexible and the reflexes normal.

The temperature was 97°F., the pulse 60, and the respirations 18. The blood pressure was not obtainable at first, but was 70 to 75 systolic, 60 diastolic, in each arm on the second hospital day.

Examination of the blood showed a white-cell count of 12,500. No other laboratory data were obtained.

An electrocardiogram showed normal rhythm with a rate of 75. In the limb leads, the T wave were low, but the ST segments remained upright, without displacement. R<sub>4</sub> was upright. There was a rather sharp, late inversion of T without displacement of the ST interval. There was no abnormal axis deviation, and the P wave and PR intervals were normal.

On the second hospital day, the temperature rose to 101°F., and the pulse rose to 100. The patient complained of headache, but felt well otherwise, the chest pain having abated. About thirty hours after entry, she suddenly gasped, took several deep breaths and expired. Immediately afterward, it was noted that the skin of the face and chest was mottled.

#### DIFFERENTIAL DIAGNOSIS

DR. WILLIAM B. BREED: Before appraising the final episode, which lasted only thirty-one hours, I should like to consider some of this patient's previous experiences in an attempt to see what can be eliminated as being nonsignificant. First of all, there is the story of recurrent fainting. "Fainting" is a term that needs defining. One type is simple fainting, which is a physiologic reaction to environment occurring in certain peo-

ple with emotional instability. Then there is the carotid sinus syndrome, which does cause syncope, but I do not see that we need more than mention it as a possibility. Also, there is the Stokes-Adams syndrome, which causes syncope and with which everyone is familiar. Paroxysmal tachycardia and fibrillation often cause syncope if they are severe enough and last long enough. I am prepared to eliminate the history of recurrent "fainting" as being significant in the patient's last illness, because we have no evidence to support any of the above diagnoses. An enlarged thyroid gland is mentioned that was considered cystic and was said to be reduced in size somewhat after the administration of small doses of thyroid. There is, however, no mention of it on physical examination here in the hospital, and I shall therefore disregard it as being of any importance. The esophageal stricture that was found by the patient's physician and was dilated may be of some consequence. It was of thirty years' duration, and for thirty years she had ground up her food, therefore, in spite of dilatation, the constriction of the esophagus must have persisted. The direct relation of that to the present episode I shall discuss later; it must be kept in mind. We do not, of course, know at what level the stricture was along the course of the esophagus.

What does the terminal episode signify? It was very sudden in onset, and a very simple affair, apparently; the patient simply became unconscious. And then after an hour, she regained consciousness, complaining of a suffocation and pressure in her chest; this sensation extended up the back to the arms and ears. It is perfectly possible that the attack of unconsciousness was not associated with any pain. On the other hand, it is also possible that the patient had a great deal of severe pain and, because of shock, became unconscious without having time to complain of it. If it was really a painless syncope, we must consider the Stokes-Adams syndrome, cerebral hemorrhage, pulmonary embolus and the carotid sinus syndrome. If the terminal episode was associated with a great deal of pain, enough to cause shock and unconsciousness, we must consider severe coronary occlusion, dissecting aneurysm of the aorta, rupture of a syphilitic aneurysm or of the esophagus into the mediastinum, subarachnoid hemorrhage and some of the paroxysmal cardiac arrhythmias.

Before trying to fit a diagnosis to this process, let us first try to make up our minds whether it was due to an intracardiac lesion or an extracardiac lesion. I am going to assume as a working hypothesis that it was an extracardiac process. I say that because the heart sounds were good,

not rapid or irregular. Also, the electrocardiogram, according to my interpretation, indicates merely some mild myocardial insufficiency, and perhaps a very old coronary occlusion. There is nothing in it to suggest recent coronary occlusion. Of course, we know that the electrocardiograph is not 100 per cent correct, but with good heart sounds, and at the same time an obliteration of peripheral arterial pulsation, I think it is fair to assume that this was an extracardiac lesion. By so doing, we automatically rule out the Stokes-Adams syndrome and coronary occlusion.

Cerebral hemorrhage must be considered, but the picture is not one of cerebral hemorrhage. The patient had recovery of consciousness after an hour, with no disturbance in reflexes. Pulmonary embolism is another possibility, but like wise there was the quick recovery after an hour, with no distention of the neck veins. To have produced unconsciousness so quickly, a massive embolism would have been necessary, and there is no evidence that it was massive. The carotid sinus syndrome is possible, but we have no evidence for it.

Could the patient have had a dissecting aneurysm of the aorta? She certainly could. That is a diagnosis that we must consider seriously, particularly with obliteration of pulse, good condition of the heart on direct examination and a negative electrocardiogram. Then the question whether there was some rupture of a viscus into the mediastinum comes up. We have no evidence of syphilitic aortitis with aneurysm.

Is it true that there is no x-ray film?

DR. TRACY B. MALLORY. There is none.

DR. BREED. I was hoping, so long as they had time for an electrocardiogram in thirty hours, that they had x-rayed the chest. A film would have been worth much more to me than an electrocardiogram.

There is no evidence of a rupture into the mediastinum. We have a story of an esophageal stricture, which might have perforated. We do not know where it was located. There may have been a hemorrhage from that stricture, or rupture and hemorrhage combined. Was there a rupture of an aneurysm somewhere in the chest? I should think it quite unlikely, if the aneurysm had ruptured, that the patient would have recovered after an hour and lived reasonably comfortably for thirty hours.

Subarachnoid hemorrhage must be mentioned because of a case that we had recently in which there was subarachnoid hemorrhage about the spinal cord only. The setup before death was so like a dissecting aneurysm that the diagnosis remained that until the post mortem examination.

It was a very unusual picture, and I should hardly think that there would be another case so soon as this. If it was subarachnoid hemorrhage, I cannot make the diagnosis. Therefore, at the moment, the decision in this case lies between a dissecting aneurysm of the aorta and rupture of the esophagus into the mediastinum, with or without hemorrhage.

I should like to comment on a few physical signs in relation to a possible perforation into the mediastinum. The cardiac dullness was of normal size, which again helps to put this in the extracardiac category. The breath sounds were tubular posteriorly, with no rales or areas of dullness in the lung fields. I am loath to accept one observation with no other pulmonary signs, and attach much significance to it. On the other hand, the possibility that something in the mediastinum collapsed the lungs and produced tubular breathing is tempting. It is a pity there was not some dullness or some other sign to go with it. I am not very familiar with perforation of the esophagus into the mediastinum. I do not believe that any of us are. We do not see it very often. We see or hear about dissecting aneurysm of the aorta much more frequently. I suppose, on the pathological chances, I should lean toward that and I think I shall, but I cannot relinquish the distinct possibility that there was a filling of the mediastinum by hemorrhage from a rupture of the esophagus.

I have never seen a caput medusae produced in thirty hours. I must assume that this patient had portal cirrhosis, with obstruction, over a period of years producing a caput medusae, and that it had no relation to the condition with which we are confronted.

I have to make one definite diagnosis. It is dissecting aneurysm of the aorta. A second diagnosis, not a very close second, is rupture of the esophagus into the mediastinum.

DR. MAURICE FREMONT-SMITH: I followed this patient for ten years, and I cannot tell you where the esophageal stricture was. A nose-and-throat man was taking care of her. I examined her a month before her last illness, and she was in good condition, felt well, and had a systolic blood pressure of 142. The story of the acute episode has a little different emphasis from what was given to it in the history.

DR. BREED: I suspected that because it is a peculiar setup.

DR. FREMONT-SMITH: I was called on the telephone by a physician who said that the patient was talking to her minister about the baptism of her grandson, very happily, and without strain, and suddenly became unconscious; *sixty seconds*,

not sixty minutes, later she was again conscious. That is my mistake in the record. She complained of severe pain, not chiefly in the chest or in the back, but in the ears; there was some pain in the chest and in the back of the neck, but not in the back. I asked the doctor whether the patient's neck was stiff, and he said, "Wait a minute, and I shall see." He told me that her neck was not stiff. He gave her morphine and sent her to the hospital. When she arrived, she was a very sick woman and was pulseless.

DR. BREED: In all the extremities?

DR. FREMONT-SMITH: I cannot tell you, since I did not check all the extremities. She was pulseless at the wrist, with a slow heart rate. The sounds were good. A loud systolic murmur, which was new and was heard also between the scapulae had developed. The patient had a fairly high white-cell count—12,000. She did not seem to have any great pain. She had been given morphine. The next morning, the resident at the Baker Memorial told me that he could feel a good pulsation in the dorsalis pedis artery, but at the same time it was impossible to feel any pulse in the wrist. At that time, the blood pressure was 110 systolic, 60 diastolic. That evening, she suddenly died.

DR. BREED: How about the tubular breathing?

DR. FREMONT-SMITH: We just noted that it was there.

DR. BREED: You did not attach any significance to it?

DR. FREMONT-SMITH: Oh yes; we did.

DR. BREED: I am sorry I made that remark about the x-ray versus the electrocardiogram.

DR. FREMONT-SMITH: Not at all. I shall tell you why it was not done. An x-ray film taken in 1940 showed the transverse measurement of the heart within normal limits. The heart showed some prominence in the region of the left ventricle. There was marked tortuosity of the aorta with a distinct bulge to the right in the ascending portion.

DR. BREED: That is comforting so far as the diagnosis I suggested is concerned. May I ask what the clinical diagnosis was at death?

DR. FREMONT-SMITH: I am sorry you asked that. Several of us had suggested dissecting aneurysm, but the final diagnosis was coronary thrombosis.

DR. ALLEN G. BRAILEY: Where did she have tubular breathing?

DR. FREMONT-SMITH: Around the angle of the left scapula.

#### CLINICAL DIAGNOSIS

Coronary thrombosis.

(Dissecting aneurysm of aorta?)

## DR. BREED'S DIAGNOSIS

Dissecting aneurysm of aorta.

(Perforation of the esophagus, with mediastinitis?)

## ANATOMICAL DIAGNOSES

Dissecting aneurysm of ascending aorta, with extension into the great vessels of neck, including complete, transverse rupture of inner aortic cylinder and rupture of outer cylinder into pericardium.

Hemopericardium, massive.

Dilatation of ovarian veins, marked.

Caput medusae.

Adenoma of thyroid gland.

## PATHOLOGICAL DISCUSSION

DR. MALLORY: At post-mortem examination, the first thing that was obvious was a greatly distended pericardium, containing several hundred cubic centimeters of dark, fluid blood in which the heart could be readily ballotted. On opening of the pericardium, it was obvious that the wall of the aorta was hemorrhagic and that there was a rent in it just a little above the level of the aortic valve, about 1 cm. in length, from which this hemorrhage into the pericardium had evidently occurred. On cutting into the aorta, the wall was found to be very thin, barely a third as thick as normal, but then much to our surprise we could not find any sort of inside of the aorta. Just above the valve, the inner segment of the aorta was torn completely across, perfectly smoothly, as if it had been cut across with an amputation knife, and for a moment or two we could not find the rest of it. Finally, it appeared up near the arch, several centimeters from the lower part. Then it became clear that this was a dissecting aneurysm extending from the aortic valve through the arch and 2 cm. down the descending aorta, and that the inner cylinder had spontaneously torn completely across, something we have not seen before. Whether the strange murmur that Dr. Fremont-Smith heard in the scapular area was produced by the free upper end of the inner cylinder flapping in the stream, I do not know. The dissection had also spread a limited distance into the innominate, both carotid and both subclavian arteries, narrowing all these vessels and thus accounting for the diminished pulse in the two arms. The heart itself was not hypertrophied. The coronary arteries were wide and capacious, with a slight amount of atheroma but no narrowing at any point.

We were naturally interested in the caput medusae that had been described. It was evident even post mortem, and to go along with it we found that the ovarian veins were markedly dis-

tended. That is usually a sign of obstruction in the caval rather than in the portal circulation, but the most careful dissection of both portal vein and the inferior cava showed absolutely no obstruction. The liver was not cirrhotic, and we have no explanation for the greatly enlarged veins in the abdominal wall and greatly enlarged ovarian veins.

DR. BREED: What was the significance of the last statement? "Immediately afterward, it was noted that the skin of the face and chest was mottled."

DR. MALLORY: I do not know.

DR. BRAILEY: Could not caput medusae be due to venous tamponade?

DR. MALLORY: These vessels must have been dilated for a considerable period. I do not believe that the patient had cardiac tamponade for a long time before death. That amount of blood in the pericardium could not have been present at the time when the examiner reported the area of the cardiac dullness as normal in size.

DR. FREMONT-SMITH: In 1939, my record states that one vein below and leading to the umbilicus was distended.

DR. BREED: Did the esophagus show anything?

DR. MALLORY: There was no stricture. There was a colloid goiter, with cystic degeneration, and it is possible that pressure from the goiter may have caused esophageal obstruction.

DR. EDWARD F. BLAND: I do not recall seeing or having read of pain in the ear with dissecting aneurysm.

DR. MALLORY: Coronary pain occasionally goes to the ear. We had one patient here who nearly had his mastoid process opened for coronary thrombosis.

A PHYSICIAN: Was the brain examined?

DR. MALLORY: Yes; it was normal.

## CASE 28112

## PRESENTATION OF CASE

*First admission.* A seventy-five-year-old German-American retired store owner was admitted to the hospital because of weakness.

He was in good health until about four months before entry, when there was gradual onset of weakness, dyspnea and a sense of pressure in the chest on effort. He had little palpitation, but no pain or orthopnea. His appetite was fair until three days before entry, when he experienced some eructation and some diarrhea, with cramps. There were no other gastrointestinal symptoms.

The family history was irrelevant. The patient had been admitted to the hospital two and a half years earlier because of a tender mass be-

neath the left nipple. A simple mastectomy was performed, a biopsy showing chronic cystic mastitis. At that time, examination of the blood showed a red-cell count of 2,600,000 with 65 per cent hemoglobin. Since this admission, the patient had lost about 30 pounds in weight.

On examination, the patient appeared pale and emaciated. His tongue was neither smooth nor red. The fingernails were flat, with longitudinal ridges. The veins over the costal margins and upper thorax appeared quite prominent. The lungs were normal. The heart was of normal size, with a faint systolic murmur at both base and apex. The abdomen was normal, except for bilateral inguinal hernias. Vibration sense and position sense were present, but diminished in the feet.

The temperature, pulse and respirations were normal. The blood pressure was 145 systolic, 80 diastolic.

Examination of the blood showed a white-cell count of 4400 with 36 per cent polymorphonuclears and 64 per cent lymphocytes, and a red-cell count of 1,910,000 with 45 per cent hemoglobin and a color index of 1.28. The cell volume was 20.7 per cent, with a volume index of 1.28. The red cells showed macrocytosis; there was a reticulocytosis of 0.6 per cent. The blood Hinton reaction was negative. The Takata-Ara and formol-gel reactions were negative. The serum protein was 5.8 gm. per 100 cc. The van den Bergh reaction was normal. The bromsulfalein test showed normal excretion of dye.

Examination of the urine at admission showed a + test for albumin, and 200 red blood cells per high-power field in the sediment. A few colonies of *Staphylococcus albus* were obtained on culture; four subsequent studies of the urine showed 17 to 25, 10 to 15, 0 and 0 red blood cells, respectively. Examination of the stools was negative. Examination of the stomach contents showed no free acid after histamine.

Roentgenographic examination of the esophagus, stomach and duodenum was negative. An intravenous pyelogram showed good excretion of dye and normal pelvis, but the calyces were obscured by intestinal shadows.

The patient was treated with six successive experimental liver-extract fractions, over a period of three months, with only minimal improvement in the blood picture. There was some relief of the weakness, however. At discharge, examination of the blood showed a red-cell count of 2,940,000 with 71 per cent hemoglobin, 33.6 per cent cell volume and 1.8 per cent reticulocytes.

*Final admission* (one and a half years later). The patient was followed in the Out Patient De-

partment and was given the usual course of intramuscular treatment with a standard commercial liver extract. Roentgenologic examination of the upper gastrointestinal tract was negative on two occasions. The red-cell count ranged between 3,000,000 and 4,400,000, until a few months before re-entry, when it slowly fell to 2,400,000 despite maintenance of regular liver extract. One week before re-entry, the patient became quite weak and drowsy, and yet was unable to sleep. He also developed increasing dyspnea on exertion, anorexia and nausea, and complained of a "brown taste" in his mouth.

On re-examination, he appeared pale, but well nourished. There was frequent stuttering, and nervous twitching. The lungs seemed emphysematous, with fine inspiratory rales at the right base posteriorly. The heart was of normal size, with a loud systolic murmur over the precordium. The veins over the upper thorax were dilated. There was pitting edema of the legs. The abdomen appeared as before. The reflexes were hyperactive, with a questionable Chvostek sign. Vibration sense was slightly diminished in the lower extremities.

The temperature was 98°F., the pulse 75, and the respirations 25. The blood pressure was 190 systolic, 90 diastolic.

Examination of the blood showed a white-cell count of 9200 with 67 per cent polymorphonuclears, and a red-cell count of 2,940,000 with 68 gm. hemoglobin, 28 per cent cell volume, a color index of 0.78, 0 per cent reticulocytes, and numerous macrocytes. The nonprotein nitrogen was 138 mg. per 100 cc.

Examination of the urine showed a ++++ test for albumin, and a sediment with 10 red cells, 2 or 3 white cells and a few finely granular casts per high-power field.

A roentgenogram of the chest showed a picture consistent with pulmonary edema on the right side.

The patient received supportive treatment, but failed rapidly. On the third hospital day, the temperature rose to 101°F., the pulse to 102, and the respirations to 35. The patient expired, apparently in uremia.

#### DIFFERENTIAL DIAGNOSIS

DR. WYMAN RICHARDSON: If there were any surgical brethren here, I should have asked them if it is customary to discharge patients with severe anemia without doing anything about it. I do not see anyone here to ask about that problem. Certainly, a man with a red-cell count of 2,600,000 requires a little thought concerning the cause of that anemia.

I might add that the mean cell volume figures

out at 108 cubic microns, macrocytic by measurement and macrocytic by observations, as it says in the next sentence, "The red cells showed macrocytosis."

There is nothing in the story of the first admission to suggest any diagnosis but pernicious anemia. The original symptoms, those of weakness, dyspnea and a sense of pressure in the chest, could well have been due to anemia alone, although we must remember that they could also have been caused by some degree of coronary disease or coronary occlusion.

The physical examination is perfectly consistent with a diagnosis of pernicious anemia, although there is nothing particularly corroborative about it. The flat fingernails with longitudinal ridges may not be of significance. They may indicate a nutritional deficiency in a rather elderly man. The fact that the vibration sense was present does not rule out the diagnosis of pernicious anemia. Diminished vibration sense in elderly people is of no diagnostic significance. In fact, it is difficult to use the vibration sense as a criterion of disease in such patients. The blood picture shows a macrocytic anemia, although not very highly macrocytic by count, if the counts are correct. The color index is high, higher than the mean cell volume indicates, and suggests that one of these two figures is incorrect. I think we can take it that the patient had a macrocytic anemia.

In an attempt to explain the urinary findings, an x-ray examination with intravenous pyelogram was done.

I am assuming that this patient had pernicious anemia, in addition to something involving the genitourinary tract that resulted in hematuria.

Have we any of the x-ray films?

Dr. TRACY B. MALLORY: Yes; we have a film, but no radiologist is here to interpret it.

Dr. RICHARDSON: I must confess that I cannot make much out of it. I can see filling on one side but not on the other. I shall not say anything more about it, but hope that one of the experts will be here before I have finished.

Another thing in the record that I think it fair to ask for and discuss is the specific gravities of the urine on the occasions when it was examined.

Dr. J. H. MEANS: I find one specific gravity of 1.022 on the first admission, and at the second admission, it ranged from 1.020 to 1.022.

Dr. RICHARDSON: It is of some importance and some interest that the specific gravity was 1.022 at the first admission.

The question of the diagnosis of pernicious anemia depends somewhat on the terminology. If one accepts as a criterion for the diagnosis the

fact that anemia is subsequently relieved by liver extract, one has a rather broad group of cases that can be called pernicious anemia. The diagnosis of pernicious anemia may be limited to a group that is due purely to some possibly congenital defect of the gastric mucosa resulting in a deficient secretion of gastric juice—so-called "idiopathic" or "agnogenic" Addisonian pernicious anemia. Furthermore, one must consider a characteristic group of pernicious-anemialike cases relieved by liver extract that are due to secondary disease elsewhere. As we go on in this case, however, if we assume that it is pernicious anemia, there is nothing to suggest any underlying disease that might produce pernicious anemia in a secondary manner.

"The patient was followed in the Out Patient Department and was given the usual course of intramuscular treatment." The usual course of intramuscular treatment was not the correct one. If the total red-cell count could not be maintained at a level of 5,000,000, he should have had an unusual course of treatment involving much larger amounts of liver. Nevertheless, there was an apparent definite response, which suggests that the diagnosis of pernicious anemia may well have been correct.

"The veins over the costal margins and upper thorax appeared quite prominent." I think that is a red herring and I shall say no more about it.

On the second entry, the quality of the anemia changed from a definitely macrocytic to a probably microcytic one, and also probably slightly hypochromic. This man had pernicious anemia, and was thoroughly treated. It is a fairly safe diagnosis for me to make because I do not believe that Dr. Mallory can check me up on it. If the patient had pernicious anemia that was not thoroughly treated, he can check me on it, but I do not see how I can lose either way. If he says that the anemia was due to some other disease, I shall counter that by saying that the change in the anemia may have been due to some other disease.

I want to mention the cystic mastitis and raise the question whether the patient had carcinoma of the breast, with widespread metastases and some involvement of the urinary tract. That seems a wild guess to make. There is no suggestion of bone-marrow replacement from the appearance of the smear, by x-ray study or by symptoms. The first thing I considered as a cause of the urinary findings and uremia was urinary obstruction. Did the patient have an enlarged prostate, with simple retention and uremia from retention? The rectal examination, I assume, was negative, and there was no evidence of bladder



enlargement; it seems unlikely that that could have been the cause of the anemia. With pernicious anemia, one must think, of course, of cord bladder, but there is no suggestion of cord involvement and I think we should rule that out. If there was obstruction, it must have been ureteral and due to tumor. That seems a rather far-fetched idea to me. The commonest cause of recurring hematuria in an elderly patient with fairly normal specific gravity is some vascular disturbance in the kidney, either repeated embolus to the kidney or nephrosclerosis of the kidney. What seems to me most probable is that this patient had rather marked generalized arteriosclerosis, which involved the kidneys more than other organs, and that the renal findings were due to a form of nephrosclerosis. It also seems probable that there was involvement of the coronary vessels, but not very marked.

One other possibility is that this patient developed pericarditis. Frequently, Dr. Mallory finds acute pericarditis that has not been suspected by the clinicians. The facts that this man's temperature rose rapidly and that he died so quickly suggest that there may have been something superimposed, and one could bring up the question of pericarditis. I see nothing to suggest it definitely.

I have left out one disease that one should always think of in the presence of anemia and uremia—plasma-cell myeloma. I considered this very strongly, but the urinary findings do not seem consistent with nephrosis. They were not those of the plugged-tubule type of renal failure, since there was too much hematuria. Also, the type of anemia was not that usually seen with bone-marrow encroachment by neoplasm in that there was not enough evidence of immature red cells or of active bone-marrow regeneration, so that I rule out myeloma on these two counts.

That leaves me with the diagnosis of pernicious anemia, which was probably not a factor in the patient's death, and generalized arteriosclerosis, more marked in the kidneys, and resulting in nephrosclerosis, uremia and death.

DR. JACOB LERMAN: I should like to ask about the pulmonary edema.

DR. RICHARDSON: I wondered about the unilateral pulmonary edema, and wondered whether I should have dismissed the question that this breast condition was a carcinoma after all.

May I see the x-ray film again? I did not visualize any picture such as that. It makes me feel badly.

DR. MALLORY: Dr. Richard Schatzki and Dr. A. Thornton Scott, a couple of years ago, noted focal pulmonary edema quite similar to this in a

number of patients with nephritis and usually with uremia.

DR. ALFRED KRANES: Dr. M. C. Sosman has also collected an interesting group of cases of unilateral edema and of one-lobe pulmonary edema in heart failure; these cases presented the most striking pictures that I have seen.

DR. RICHARDSON: One of my rules is not to change my mind at the last moment. I am not going to now.

DR. MALLORY: Dr. Means, have you anything to add?

DR. MEANS: We made clinically about the same diagnosis that Dr. Richardson did. I think there is no more to be said about that.

I am interested in the x-ray picture. I was thinking of Dr. Schatzki and Dr. Scott's observations and also the demonstrations that Dr. Frank Fremont-Smith made a number of years ago that edema in general is closely related to body position. It would be interesting to take pictures of such patients, having them lie for a while first on one side and later on the other to see if the picture changed. It is a new concept to find edema in the middle of the lung field, and it may be because the patients are lying down, and hence this area may be the dependent portion.

DR. MALLORY: I shall disagree with that in a moment.

DR. LERMAN: This patient had a hematuria of 200 red cells in the first sediment. That seems to be a good deal for mere vascular disease of the kidney. I am rather inclined to some malignant process in the bladder or in the kidney itself.

DR. RICHARDSON: I think that hematuria occurs either with embolism or with vascular disease. I certainly have seen it.

#### CLINICAL DIAGNOSES

Pernicious anemia.

Uremia.

Pulmonary edema.

#### DR. RICHARDSON'S DIAGNOSES

Pernicious anemia.

Nephrosclerosis, with uremia.

#### ANATOMICAL DIAGNOSES

Subacute glomerulonephritis.

(Pernicious anemia.)

Focal pulmonary hemorrhage.

Bronchiectasis, right middle lobe.

Arteriosclerosis, moderate, aortic and coronary

Hypertrophy of the heart.

Operative scar: left mastectomy.

Inguinal hernias, bilateral.

## PATHOLOGICAL DISCUSSION

DR. MALLORY: The autopsy showed primary disease of the kidneys, which weighed 275 gm. and were rather pale. The surfaces were still fairly smooth, with beginning granulation. The microscopic examination showed a subacute or very early chronic glomerulonephritis. How long the patient had it, it would be difficult to estimate on histologic grounds alone; I should think that it was not over a period of two years. It developed some time between the mastectomy and either the first or the second subsequent admission. Whether he had it at the first re-entry, I cannot be sure.

The heart was slightly hypertrophied. The coronary arteries showed atheroma, but no point of occlusion. The lungs showed focal bronchiectasis and also a lesion that we have seen a number of times in nephritis and to my eye is indistinguishable from what we occasionally see in cases of acute rheumatic fever. It has been described clinically as pulmonary edema, but under the microscope it is predominantly pulmonary hemorrhage. There are almost always foci of organization by connective tissue, which are usually found in the respiratory bronchioles. Many of these cases could be and, I believe, sometimes

have been described as bronchiolitis obliterans. It is certainly not pulmonary edema such as one sees in the average cardiac patient. The alveoli are full of red cells; there is a moderate amount of fibrinoid material, usually at the periphery. Usually, there are no leukocytes. To my eye, it is as yet indistinguishable from what has been described as rheumatic pneumonia.

The bone marrow is the only thing that could possibly substantiate or deny Dr. Richardson's diagnosis of pernicious anemia. I do not consider it very conclusive. It was rather more hyperplastic than the marrow of chronic nephritis usually is, with a distinctly greater degree of proliferation of the red cells than is seen in the average case of nephritis, not a clearcut picture of pernicious anemia. On the other hand, the alterations from what one ordinarily meets in chronic nephritis were definitely in the direction of pernicious anemia. Consequently, I am inclined to think it did show some effect of that disease as well.

DR. MEANS: Are you suggesting that the findings that Dr. Schatzki and Dr. Scott described as edema were not edema?

DR. MALLORY: Yes.

DR. MEANS: That is all right then. You can fight that out with Dr. Schatzki and Dr. Scott.

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established in 1828

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND  
PUBLISHED UNDER THE JURISDICTION OF THE  
COMMITTEE ON PUBLICATIONS

Official Organ of  
THE MASSACHUSETTS MEDICAL SOCIETY  
and  
THE NEW HAMPSHIRE MEDICAL SOCIETY

## EDITORIAL BOARD

Joseph Garland, M.D.	Stephen Rushmore, M.D.
William B. Breed, M.D.	Henry R. Viets, M.D.
George R. Minot, M.D.	Robert M. Green, M.D.
Frank H. Lahey, M.D.	Charles C. Lund, M.D.
Shields Warren, M.D.	John F. Fulton, M.D.
George L. Tobey, Jr., M.D.	A. Warren Stearns, M.D.
C. Guy Lane, M.D.	Dwight O'Hara, M.D.
William A. Rogers, M.D.	Chester S. Keefer, M.D.

## ASSOCIATE EDITORS

Thomas H. Lanman, M.D.	Donald Munro, M.D.
Henry Jackson, Jr., M.D.	

Walter P. Bowers, M.D., EDITOR EMERITUS

Robert N. Nye, M.D., MANAGING EDITOR

Clara D. Davies, ASSISTANT EDITOR

SUBSCRIPTION TERMS: \$6.00 per year in advance, postage paid, for the United States (medical students, \$3.50 per year); Canada, \$7.04 per year, Boston funds; \$8.52 per year for all foreign countries belonging to the Postal Union.

MATERIAL for early publication should be received not later than noon on Friday.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston, Massachusetts.

## A CHANGE IN THE BOARD OF REGISTRATION IN MEDICINE

ON February 17, 1942, Dr. Stephen Rushmore resigned from the position of secretary of the Massachusetts Board of Registration in Medicine to accept the position of dean of the School of Medicine of Middlesex University. Governor Saltonstall has appointed Dr. H. Quimby Gallupe, of Waltham, to fill the vacancy, and on February 26, at a meeting of the Board, Dr. Gallupe was elected secretary. As secretary, Dr. Gallupe has three additional *ex-officio* positions: he is chairman of the Approving Authority for Colleges and Medical Schools and secretary of the Board of Registration of Nurses and of the Approving Authority for Schools of Nursing.

As the holder of these various positions, Dr. Gallupe will be faced with many important problems. One of the most difficult is a decision that must sometime be made by the Approving Authority for Colleges and Medical Schools. It is well known that two medical schools and one osteopathic school in Massachusetts are not approved by their respective national societies; however, no public statement concerning their status, even in part, has been issued by the Approving Authority. Since this law went into effect in 1941, all members of the present first-year classes of these schools are receiving a medical education that may prove to be futile, and it seems likely that an embarrassing situation will arise. If the eventual decision is adverse, the students will feel aggrieved, and justly so, that the judgment—at least that covering their years of attendance—had not been passed sooner. If the decision is favorable, some people will undoubtedly question the legality of a retroactive verdict in such a situation, claiming that only the part of the students' education should be recognized that occurred after the decision had been made. It is apparently the clear intent of the law that, from its effective date of operation, no medical education shall be considered valid unless it has been gained in an approved school.

Dr. Gallupe's experience and training, not only in the practice of medicine but also in the affairs of the Massachusetts Medical Society, are such that the public and the profession can have confidence in those boards of which he is now an influential member. The Governor, the Governor's Council and the Board of Registration in Medicine are to be congratulated on having made an excellent appointment to a very responsible position.

## CIVILIAN DEFENSE

OUR country, long before the attack on Pearl Harbor, had begun to realize the necessity for civilian defense. Air-raid wardens were in training, the versatility of the triangular bandage was

a matter of tea-table discussion, new and strange feminine uniforms had made their appearance, and Red Cross headquarters in every direction hummed like sawmills. Despite our own relative insularity, we were aware that events were stirring. We knew, secretly, that "it couldn't happen here," but we almost wished that it could, in a mild sort of way, so that we might show how America handled these things.

And then came Pearl Harbor, like a rash and a fever, and we knew that we, too, had the epidemic disease; we were a nation at war. For those who were unable, by reason of age, sex or other incapacity, to join the armed forces, some other quick emotional outlet was necessary; the important thing was to rally in some way to the country's defense—to be doing something.

As a result of this enthusiastic and heartening response, civilian defense has come a long way toward becoming an effective organization: an organization that will, we trust, have little occasion to be used, but one whose serious existence is absolutely mandatory. Committed to this work are our air-raid wardens, our auxiliary fire departments, our lonely watchers of the midnight skies and, above all, those necessary defenders of the commonweal who daily fight the battles of the committees.

There is some vitally essential activity for every individual to share, in addition to paying his taxes and buying defense bonds, but it might be well to remind ourselves, occasionally, that these cannot all be dramatic or obviously heroic activities. We are engaged now in a race toward a goal of production. If we win it, democracy may yet be saved; if we fail, the future looks dismal enough. As impressive as the most military of our civil uniforms and far surpassing them in numbers must be the aprons and the overalls.

When the first-aid fever has died down a bit, when the last sacroiliac strain, the result of over-zealously applied artificial respiration, has been

strapped, when the last broken rib has mended and when the last breathless housewife has received her certificate, we may recall the sober fact that not one in a thousand of our first aiders will ever have occasion to adjust a traction splint or save a life by applying a skilful finger to a pressure point, but that everyone who has taken the equivalent course in nutrition or home nursing will probably have plenty of opportunity to employ the knowledge gained before the year is out. This war will be won by having the greatest number do that for which there is the greatest need and by having each willing to perform faithfully that service for which each is best fitted.

## MEDICAL EPONYM

MURPHY DRIP

Dr. John Benjamin Murphy (1857-1916) spoke on "Diffuse Suppurative Peritonitis" before the American Association of Obstetricians and Gynecologists on September 21, 1906. His remarks included some mention of his new method of proctoclysis, and in the subsequent discussion he described it as quoted below from the *Transactions of the American Association of Obstetricians and Gynecologists* (19: 184, 1906):

An ordinary vaginal douche tip should be used, with three openings, so that the water can flow into one and the intestinal gas come out of the other. If we use a single opening tip, gas will not bubble back into the can, and the passing of gas is important, otherwise the fluid will be expelled in the bed when the patient attempts to pass the gas. The elevation of the can should be from four to six inches above the anal level. The nurse must be instructed to watch the patient closely and not allow any more than one pint and a half of the saline solution to flow in forty minutes to one hour. The tube can be strapped permanently to the leg of the patient with adhesive plaster, the fountain syringe being at the head of the bed, and a hot water bag used to keep the solution warm. Every two hours the nurse pours in hot saline water. There is no irritation of the rectum. The patient may go to sleep while the irrigation is being carried on, as the tube is not taken out for days. It is merely absorption of the fluid by the bowel. The speed of the flow must not be controlled by a forcep in the tube, but by the elevation of the can.

R. W. B.

## MASSACHUSETTS MEDICAL SOCIETY

## COMMITTEE ON MATERNAL WELFARE\*

CASE HISTORY: COMPLETE SEPARATION OF  
PLACENTA, FOLLOWED BY DEATH

A thirty-eight-year-old para V called her physician because of some bloody discharge when she was about seven months pregnant. The previous history was irrelevant; the patient had had no serious illnesses. Her four previous pregnancies and deliveries had all been normal.

She was first seen during this pregnancy when about three months along and went to her physician every four weeks thereafter until the onset of the present complication. The blood pressure and urine were reported to be normal, there had been no edema, and the blood Wassermann reaction was negative. There had been an interval of four weeks between the last visit and the onset of symptoms. On examination, the abdomen was boardlike. The amount of external bleeding was very slight. The patient was immediately sent to the hospital, where she arrived one and a quarter hours later. The fetal heart was not heard. The blood pressure on entry was 66 systolic, 40 diastolic, but later rose to 150 systolic, 90 diastolic. A transfusion was immediately given. Vaginal examination showed that the patient was not in labor. A Spanish windlass was applied. The membranes were not ruptured. The cervix and vagina were not packed. No other treatment was instituted, and death occurred six hours after admission. No autopsy was performed.

*Comment.* This is a typical case of complete premature separation of the placenta. It is quite probable that during the month between the last visit and the onset of bleeding, this patient's blood pressure rose and albumin appeared in the urine. The fatal outcome emphasizes the need of more frequent urinalyses and prenatal visits in the last trimester of pregnancy. The blood pressure on admission shows that this patient had bled tremendously inside the uterus and was in a very serious condition. The treatment can be criticized only in that the membranes were not ruptured and that there was no cervical or vaginal packing. Abdominal deliveries on patients with completely separated placentas who are in such poor condition as this patient was, are but adding insult to injury and are not advisable. Such fatalities can be prevented only by more intelligent co-operation between patient and physician and more frequent prenatal visits and urinalyses after the seventh month.

\*A series of selected case histories will be published weekly. Comments and questions by subscribers are solicited and will be answered by members of the committee. Letters should be addressed to the secretary, Dr. Raymond S. Titus, 330 Dartmouth Street, Boston.

## DEATHS

**HARTWELL** — **WILLIAM W. HARTWELL, M.D.**, of Malden, died March 1. He was in his sixty-ninth year. Born in Woburn, Dr. Hartwell received his degree from Harvard Medical School in 1900. He served as city physician in Malden for several years and as medical examiner of the Malden Board of Health. He was a member of the Massachusetts Medical Society and the American Medical Association.

He is survived by two sons.

**REED** — **VICTOR A. REED, M.D.**, of Methuen, died February 24. He was in his seventy-fourth year.

Born in Dixmont, Maine, the son of William E. and Elizabeth Ferguson Reed, Dr. Reed completed his preparatory education at the Hampden High School and studied for two years at Colby College in Waterville, Maine. He received his degree from Harvard Medical School in 1897 and did postgraduate work at the New York Polyclinic Medical School and Hospital.

Dr. Reed served as a line officer in the National Guard in 1902 and later as a captain in the Medical Corps at Fort Williams, Portland, Maine. He was a member of the staff of the Lawrence General Hospital, and was a former medical examiner for the fifth Essex district. He was a fellow of the Massachusetts Medical Society and the American Medical Association.

He is survived by his widow, Mrs. Josephine B. Reed, and a daughter, Mrs. J. Alexander McWilliams, of Chicago.

## WAR ACTIVITIES

## SELECTIVE SERVICE SYSTEM

## PHYSICAL REHABILITATION PROGRAM

Tests of a physical rehabilitation program, intended to make many registrants who were rejected because of minor physical defects fit for active military service, have been authorized in Maryland and Virginia, according to a recent release from the National Headquarters, Selective Service System. Authorization of the rehabilitation programs in the two states marks the beginning of a long-planned nation-wide physical rehabilitation campaign. When the results of these pilot tests are evaluated, a date for the inauguration of the inclusive program will be set. Only those registrants whose disabilities are certified by the Army as being remediable will be eligible to undergo treatment.

As one of the first steps in the Maryland and Virginia test programs, the director of Selective Service System in each state will submit to National Headquarters lists of physicians and dentists qualified to correct physical defects of registrants. Physicians and dentists designated to render these authorized professional services will be paid by the federal government. Any physician or dentist may apply to be included in the rehabilitation program and can obtain the necessary application form from his local board.

## CORRESPONDENCE

"THE POLITICAL LIFE OF THE  
AMERICAN MEDICAL ASSOCIATION"

*To the Editor:* Just before Christmas, I received a catalog from the Harvard University Press. One item listed therein particularly caught my eye — *The Political Life of the American Medical Association*, by Oliver Garceau, instructor in government at Harvard. I bought a copy, and have just finished reading it. Having found it highly

interesting informative and possibly important, I decided to see what reviewers had to say about it. I first encountered the contribution in the Book Reviews column of your issue of January 1. I must confess that I was taken aback by the ineptitude of this statement. It is hardly a review of Mr Garceau's book. It is rather a blanket condemnation.

Your reviewer applies various derogatory adjectives of which jejune is perhaps the prize. Jejune, like jejunum comes from the Latin *jejunus*, meaning empty, dry or barren and, in my opinion, is applicable to your so-called review but not at all to Mr Garceau's book, which, whatever else it may be, is certainly not empty, dry or barren.

Your reviewer also accuses Mr Garceau of having such a biased point of view that it takes away any force that he might have in argument. This accusation strikes me as preposterous. The work is not an argument, it is simply an analysis by a student of government of a politico-social phenomenon of some prominence. It discovers many good features, as well as some bad ones in organized medicine. There is no reason on earth why a student of government, or politics, should have any bias about such a matter, nor could I find in his book any evidence that he has. I, for one, am convinced that his approach is thoroughly objective, and that his facts are probably approximately correct. I do not know him, but that is the impression that I get from reading his book.

It seems to me that what your reviewer has chiefly succeeded in doing is to disclose himself as the biased one, not Mr Garceau. I do not know who he is but I should guess that he is one of those 'stalwarts' of organized medicine whom Mr Garceau identifies as believing that the layman is unfit to have an opinion in medical matters and extends this value judgment to include medical politics and medical economics, fields where it might almost be said the doctor is inherently unfit.

Differing diametrically from your reviewer on the merit of Mr Garceau's work, I should like, through your correspondence column to offer to the members of our profession, advice opposite to his, namely, that they read this book and form their own opinion of it afterwards.

J H MEANS

Massachusetts General Hospital  
Boston

## BOOK REVIEW

*The Foot and Ankle. Their injuries, diseases, deformities and disabilities with special application to military practice.* By Philip Lewin, MD. Second edition. 8°, cloth 660 pp., with 304 illustrations. Philadelphia: Lea and Febiger, 1941. \$9.00.

From the publishers' point of view, this second edition of Philip Lewin's book on the foot and ankle is admirably done although somewhat awkward to handle. One wonders what would happen should the author ever be tempted to write a textbook on orthopedic surgery. Six hundred and eighteen pages on the foot and ankle alone could hardly escape being a mere repository for the gleanings of an encyclopedic mind. No one can deny that the work has not been most thoroughly done.

So many new surgical procedures have come out and are continually being added to, that scarcely any of them have had time enough to warrant their acceptance or rejection. Kridas's operation (page 176) for metatarsalgia is a case in point. If one wishes a reference book in which is enumerated almost every kind of treatment

that has been proposed, without critical consideration of its applicability, this volume is the one to buy. The experienced orthopedic surgeon may be trusted to recognize what procedures are feasible, but to the young and inexperienced, something more is needed than a catalogue of the ships. Had the author drawn on his wide clinical experience to aid the audience he is addressing through this volume in selecting the tried and proved techniques, he would have rendered a greater service and done so in much less space.

## Erratum

In the review of the book *Oral Pathology. A histological, roentgenological and clinical study of the diseases of the teeth, jaws and mouth*, which appeared in the February 19 issue of the *Journal*, the authors were listed as Kurt H Thoma, DMD and Charles A Brackett, DMD. The author is Dr Thoma, who is professor of oral surgery and Charles A Brackett Professor of Oral Pathology, Harvard University.

## NOTICES

### TUFTS COLLEGE MEDICAL SCHOOL ALUMNI ASSOCIATION

Dr Frank H Lahey, president of the American Medical Association, will be the guest speaker at the annual Tufts College Medical School Alumni Dinner, at 7 p.m. on Wednesday, March 23, at the Hotel Somerset. His subject will be *The Doctor's Place Today*. Dr James W Manary, superintendent and medical director of the Boston City Hospital will preside.

Other speakers on the program are Dr A K Paine, president of the Alumni Association who will discuss the Association's activities; Dr Leonard Carmichael, president of Tufts College, who will report on the medical school fund; Dr Priscilla White, who will speak on *The Woman Physician*; Dr Frank R Ober, who will extend the greetings of the Massachusetts Medical Society; and Dr Roy J Heffernan, who will speak on *The Twenty Five Year Class*.

The dinner will be preceded by a business meeting at 6.15 p.m.

### ROBERT DAWSON EVANS MEMORIAL LECTURE

Dr William Dock, professor of pathology at Cornell University Medical College, will give the Robert Dawson Evans Memorial Lecture on Friday, March 27, at 8.15 p.m. in the Evans Memorial Auditorium, 78 East Concord Street, Boston. His subject will be *Albuminuria and Associated Renal Changes*.

Physicians and medical students are cordially invited to attend.

### BOSTON LYING IN HOSPITAL

A meeting of the Journal Club of the Boston Lying in Hospital will be held in the lecture hall of the hospital on Wednesday, March 18, at 8.15 p.m. Dr Robert E Gross will speak on *Surgical Problems of the Newborn*.

Physicians and medical students are cordially invited to attend.

### CARNEY HOSPITAL

The monthly clinical meeting and luncheon of the Carney Hospital will be held in the hospital auditorium on Monday, March 16 at 11.30 a.m.

## PROGRAM

Use of Spinal Anesthesia in Obstetrics. Dr. Joseph Ferrone.

Treatment of Hydrocephalus in Obstetrics, with Report of a Case. (With Films.) Dr. Arthur Gorman.

Rupture of Uterus. (With Films.) Dr. Cornelius T. O'Connor.

Physicians and medical students are cordially invited to attend.

## MASSACHUSETTS GENERAL HOSPITAL

A meeting of the Hospital Research Council will be held in the Bigelow Amphitheater of the White Building on Tuesday, March 24, at 5 p.m.

## PROGRAM

Effects of Rebreathing on Sighing Respiration and Anxiety Symptoms in Patients with Anxiety Neurosis. Drs. S. Cobb and M. Cohen.

Rheumatic Fever and Heart Disease: Special clinical features from a completed ten-year study of 1000 patients. Drs. E. F. Bland and T. D. Jones.

An Epidemic of Rheumatic Fever. Dr. T. D. Jones.

## NEW ENGLAND ROENTGEN RAY SOCIETY

A meeting of the New England Roentgen Ray Society will be held in John Ware Hall, Boston Medical Library, on Friday, March 20. There will be an x-ray conference from 4:30 to 6:00 p.m., followed by a round-table discussion on radiation therapy, conducted by Dr. Frederick W. O'Brien. At 8:00 p.m., the following program will be presented:

Sarcoid and Erythema Nodosum. Drs. Charles A. Janeway, Orville T. Bailey and Merrill C. Sosman.

Periarteritis Nodosa and Lupus Erythematosus Disseminata. Drs. Eugene A. Stead, Orville T. Bailey and Merrill C. Sosman.

Discussion. Drs. Chester S. Keefer, Tracy B. Mallory and Aubrey O. Hampton.

## NEW ENGLAND PATHOLOGICAL SOCIETY

There will be a meeting of the New England Pathological Society at the Peter Bent Brigham Hospital on Thursday, March 19, at 8 p.m. The program will be presented by the Department of Legal Medicine of the Harvard Medical School.

## PROGRAM

The Law and the Pathologist. Dr. Hubert W. Smith.  
An Experimental Study of the Chemical Changes which Occur in the Blood as the Result of Death by Drowning. Drs. Walter W. Jetter and Alan H. Moritz.

Adaptive Intimal Changes which Occur in Arteries Following Localized Circulatory Stasis. Dr. Alan R. Moritz.

Medicolegal Tests for the Identification of Seminal Fluid. Dr. Otto J. Pollak.

An Experimental Investigation of the Stability and Distribution of Carboxyl Hemoglobin after Death, with Particular Reference to the Difficulties Sometimes Encountered in the Case of Incinerated Bodies. Dr. Herbert S. Breyfogle.

The Fauna of Putrefaction and Its Potential Usefulness in Establishing the Time of Death. Dr. J. C. Bequaert.

## MASSACHUSETTS TUBERCULOSIS LEAGUE

The annual meeting of the Massachusetts Tuberculosis League will be held on Thursday, March 26, at the Boston Sanatorium, Mattapan.

## PROGRAM

10 a.m. Round-Table Conference on Tuberculosis Programs in Boston. Drs. John A. Foley, Harry Goldman, James A. Keenan and Cleaveland Floyd, and the Misses Hazel Wedgwood and Dorothy Carter; Dr. George L. Gately, chairman.

11:45 a.m. Business meeting.

12:45 p.m. Luncheon.

2 p.m. Round-Table Conference on Tuberculosis Prevention through Readjustment as a War Service. Messrs. Arthur W. Gerness and John H. McFarland, Mrs. Mildred S. Jeynes, and Drs. William R. Martin and Frederick L. Bogan; Dr. Henry D. Chadwick, chairman.

The charge for luncheon will be 90 cents per person. Reservations should be sent to: Massachusetts Tuberculosis League, 1148 Little Building, Boston. Tel. HAN 5480.

## JEWISH MEMORIAL HOSPITAL

A diagnostic therapeutic conference will be held at the Jewish Memorial Hospital on Thursday, March 19, at 11 a.m. Dr. William P. Murphy will speak on "Blood Diseases."

Physicians and medical students are cordially invited to attend.

## NEW ENGLAND SOCIETY OF PHYSICAL MEDICINE

A regular meeting of the New England Society of Physical Medicine will be held at the Hotel Kenmore, Boston, on Wednesday, March 18, at 8 p.m. Colonel Winthrop Adams will speak on "Physical Medicine in Wartime." A council meeting will be held at 6 p.m., followed by an informal dinner in the Empire Room at 6:30 p.m.

All interested physicians are cordially invited to attend this meeting.

## EVANS MEMORIAL HOSPITAL

A research conference will be held in the auditorium of the Evans Memorial Hospital on Monday, March 23, at 5 p.m. Dr. Franz J. Ingelfinger will speak on "Studies on the Absorption Defect in Sprue."

## FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY

The Federation of American Societies for Experimental Biology will meet in Boston from March 31 to April 4. Registration will start on Tuesday, March 31, at 10 a.m. at the Hotel Statler. The headquarters, session dates and

(Notices continued on page xi)

# The New England Journal of Medicine

Copyright, 1942, by the Massachusetts Medical Society

VOLUME 226

MARCH 19, 1942

NUMBER 12

## VITAMIN C AND WOUND HEALING\*

### I. Experimental Wounds in Guinea Pigs

MARSHALL K. BARTLETT, M.D.,† CHESTER M. JONES, M.D.,‡ AND ANNA E. RYAN, B.A.§

BOSTON

THAT the tensile strength of healing wounds is lowered in the presence of scurvy in guinea pigs was established by Lanman and Ingalls<sup>1</sup> in 1937 and confirmed by Taffel and Harvey.<sup>2</sup>

The work of Bessey<sup>3</sup> has provided a satisfactory method of determining the ascorbic acid content of tissues, and the experiments reported in this study were undertaken to determine the concentration of vitamin C in healing wounds in guinea pigs under a variety of dietary conditions, and to correlate the ascorbic acid content with the tensile strength of these wounds.

#### METHODS

After suitable dietary preparation, under ether anesthesia, a midline abdominal incision was made in each guinea pig, extending from the xiphoid to a point just below the umbilicus. A strip of tissue adjacent to the wound, consisting of the full thickness of the abdominal wall and weighing about 2 gm., was excised for ascorbic acid assay. This specimen is called "control tissue" in the various tables that appear below. The peritoneum and muscular layers were then closed in a single layer with a running suture of fine silk, and the skin was closed in a similar manner.

At the end of a suitable period of wound healing, the skin sutures were removed, and the healing wound excised, including the full thickness of the abdominal wall in a strip about 0.6 cm. in width, with the line of incision running down its center. This tissue was assayed for ascorbic acid and appears under the heading "abdominal scar" in the tables. Portions of abdominal wall adjacent to the excised scar and similar portions at a distance from it were removed for comparative assay.

These appear as "adjacent abdominal wall" and "distant abdominal wall" in the tables. Vitamin C determinations were also done on the livers and kidneys of these animals.

The term "house diet" is used to describe the usual one of grain, hay, green vegetables and water. As a scorbutic diet, we have found the one described by McCullough<sup>4</sup> most satisfactory. Animals can be successfully maintained on this diet for considerable periods. Its percentage composition is as follows:

Whole-milk powder (inactivated at 120°C. for two hours)	40.5
Ground, rolled oats	25.0
Bran	25.0
Dried brewer's yeast	5.0
Cod-liver oil	3.0
Sodium chloride	1.0
Ferric citrate	0.5

To afford a high intake of vitamin C, either the house diet or the scorbutic diet was supplemented by 33 mg. of ascorbic acid in 5 cc. of water twice daily. This solution was fed to the animals by medicine dropper and was usually taken without difficulty. The dosage is considerably larger than that reported by Zilva<sup>5</sup> and by Ecker and Pillemer<sup>6</sup> as necessary to maintain tissue saturation in the guinea pig, and should certainly provide an excess of ascorbic acid even in the presence of a possible increased demand due to the healing wound.

#### RESULTS

##### Control Animals

The ascorbic acid content of various animal tissues has been studied by several workers.<sup>7-15</sup> However, because of differences in methods of assay and varying experimental conditions, the results of these investigations are not strictly comparable to the studies reported here, and will not be referred to in detail.

\*From the Medical and Surgical services, Massachusetts General Hospital.

†Assistant surgeon, Massachusetts General Hospital.

‡Clinical professor of medicine, Harvard Medical School; physician, Massachusetts General Hospital.

§Technician, Massachusetts General Hospital.



To obtain control figures, the ascorbic acid content of the abdominal wall was determined on 19 guinea pigs on a scorbutic diet for two weeks or more. The average concentration was 0.23 mg. per 100 gm. Similar determinations were made on 17 animals on a high vitamin C diet for two weeks or more, and it was found that the average level was 1.51 mg. per 100 gm.

We believe two weeks to be an adequate period to establish a tissue level of ascorbic acid on a given diet. The results of assays of the abdominal wall, liver and kidney, made at intervals of one, two and three weeks, on animals on a high or low vitamin C intake appear in Table 1. There

TABLE 1. Tissue Assays of Ascorbic Acid on Control Animals on Diets Varying in Vitamin C Content.

WEEKS	ABDOMINAL WALL mg./100 gm.	LIVER mg./100 gm.	KIDNEY mg./100 gm.
HOUSE DIET			
3+	0.47	2.82	1.11
3+	0.65	1.82	1.35
HIGH VITAMIN C DIET			
1	1.99	19.35	5.57
2	2.28	11.26	5.94
3	2.52	14.41	6.49
SCORBUTIC DIET			
1	0.31	1.42	1.49
2	0.08	0.43	2.99
3	0.59	1.13	0.21

seems to be no essential difference between the levels attained at the end of one week and those at longer intervals. We have therefore taken a period of two weeks as being adequate to establish tissue levels of ascorbic acid corresponding to the intake of vitamin C.

It is interesting that the house diet, which has apparently been entirely satisfactory over a period of years, and on which guinea pigs thrive for indefinite periods, produces tissue levels only slightly higher than the scorbutic diet. This wide variation in the amount of ascorbic acid necessary for protection against scurvy and that required to produce tissue saturation has been stressed by Zilva<sup>5</sup> and by Ecker and Pillemer.<sup>6</sup>

Experimental Animals

*Preoperative and postoperative scorbutic diet.* Ten guinea pigs were maintained on a scorbutic diet for two weeks. At the end of this time, an abdominal incision was made, and a control biopsy obtained. The scorbutic diet was continued postoperatively.

At the end of arbitrary intervals, varying from four to fourteen days, the animals were killed and tissue assays done, as previously described. The results of these determinations are shown in Table 2.

The average postoperative interval was nearly ten days, and there was no significant variation in

the tissue levels at the shorter and longer postoperative intervals. All the tissue levels were low, and the averages show that there was no increase in the concentration of ascorbic acid in the heal-

TABLE 2. Assays of Ascorbic Acid in Tissues of Animals on a Preoperative and Postoperative Scorbutic Diet.

CONTROL TISSUE	POSTOP- ERATIVE DAY ON WHICH ANIMAL WAS KILLED	AUTOPSY TISSUES				
		AB- DOM- INAL SCAR	ADJA- CENT AB- DOM- INAL WALL	DIS- TANT AB- DOM- INAL WALL	LIVER	KIDNEY
ABDOMINAL WALL		mg./ 100 gm.	mg./ 100 gm.	mg./ 100 gm.	mg./ 100 gm.	mg./ 100 gm.
0.14	4	0.19	0.33	—	1.15	0.16
0.28	4	1.13	0.14	0.08	1.30	0.98
0.15	5	0.04	0.21	—	1.19	0.34
0.99	9	0.24	0.11	—	0.73	0.16
0.21	9	0.18	0.05	—	0.58	0.32
0.28	9	0.27	0.20	0.25	0.63	0.75
0.09	14	0.10	0.17	—	0.44	0.59
0.10	14	0.33	0.01	—	0.81	—
0.09	14	0.12	0.06	0.23	0.59	0.19
0.15	14	0.28	0.16	0.22	1.13	0.39
Average						
0.25	9.6	0.29	0.14	0.20	0.86	0.43

ing wound. Assays of the abdominal wall, both adjacent to and at a distance from the healing area, showed some decrease below the level found in the control biopsy taken at operation.

*Preoperative and postoperative high vitamin C diet.* After a preliminary period of two weeks

TABLE 3. Assays of Ascorbic Acid in Tissues of Animals on a Preoperative and Postoperative Diet High in Vitamin C.

CONTROL TISSUE	POSTOP- ERATIVE DAY ON WHICH ANIMAL WAS KILLED	AUTOPSY TISSUES				
		AB- DOM- INAL SCAR	ADJA- CENT AB- DOM- INAL WALL	DIS- TANT AB- DOM- INAL WALL	LIVER	KIDNEY
ABDOMINAL WALL		mg./ 100 gm.	mg./ 100 gm.	mg./ 100 gm.	mg./ 100 gm.	mg./ 100 gm.
1.08	4	7.39	4.93	—	11.73	6.92
2.24	4	6.74	3.67	—	15.21	4.85
1.28	4	4.63	3.18	2.72	4.88	3.74
1.36	9	6.83	2.96	2.97	18.16	4.53
1.51	9	9.71	4.70	5.31	22.02	6.05
1.90	9	6.15	1.85	1.69	5.53	4.14
1.23	9	5.62	3.15	3.09	4.68	2.88
2.09	14	6.70	3.39	2.71	7.63	3.98
0.69	14	7.15	1.21	1.07	4.22	1.99
2.29	14	4.38	2.29	2.04	1.77	1.01
Average						
1.57	9.0	6.53	3.13	2.70	9.58	4.01

on a high ascorbic acid intake, 10 animals were subjected to the same operative procedure as that in the preceding group. At postoperative intervals of four to fourteen days, with an average of nine days, the animals were killed and the tissue assays of ascorbic acid were done. The results appear in Table 3.

Again, there was no significant difference in the results obtained at the shorter and longer post-

operative intervals. However, there was a marked increase in ascorbic acid content in the healing wound over the concentration in the control biopsy of the abdominal wall. The tissue of the abdomen

TABLE 4. Assays of Ascorbic Acid in Tissues of Animals on a Preoperative Scorbutic Diet and a Postoperative High Vitamin C Diet.

CONTROL TISSE	POSTOP ERATIVE DAY ON WHICH ANIMAL WAS KILLED	AUTOPSY TISSUES					
		AB- DOM- INAL SCAR	ADJA- CENT AB- DOM- INAL WALL	DIS- TANT AB- DOM- INAL WALL	LIVER	KIDNEY	
mg / 100 gm		mg / 100 gm	mg / 100 gm	mg / 100 gm	mg / 100 gm	mg / 100 gm	
0.21	4	4.53	2.42	2.77	7.91	4.23	
0.15	9	3.90	1.37	1.22	4.47	2.28	
0.07	9	5.13	2.73	2.87	0.51	2.18	
0.16	9	4.32	1.99	1.63	5.03	2.59	
0.09	14	4.04	2.50	0.98	2.89	1.15	
0.27	14	3.81	1.83	2.49	2.74	2.53	
Average 0.16	9.9	4.29	2.14	1.99	3.93	2.58	

inal wall adjacent to the healing wound, taken at autopsy, showed a considerable increase in vitamin C content, and a slight increase was shown in the abdominal wall at a distance from the wound. The assays of liver and kidney showed levels uniformly much higher than those obtained on similar animals on a scorbutic diet, but not quite so high as those in the 3 animals on a high ascorbic acid diet on which no operation was done (Ta-

TABLE 5. Assays of Ascorbic Acid in Tissues of Animals on a Preoperative High Vitamin C Diet and a Postoperative Scorbutic Diet.

CONTROL TISSE	POSTOP ERATIVE DAY ON WHICH ANIMAL WAS KILLED	AUTOPSY TISSUES				
		AB- DOM- INAL SCAR	ADJA- CENT AB- DOM- INAL WALL	DIS- TANT AB- DOM- INAL WALL	LIVER	KIDNEY
mg / 100 gm.		mg / 100 gm.	mg / 100 gm.	mg / 100 gm.	mg / 100 gm.	mg / 100 gm.
0.0	4	0.42	0.17	0.33	0.18	0.77
0.77	9	0.82	0.38	0.40	1.78	0.73
1.05	9	0.11	0.18	0.14	0.66	0.75
1.35	14	0.59	0.22	0.27	0.54	0.44
Average 0.79	9.0	0.49	0.24	0.29	0.79	0.67

ble 1). The small number of animals in the last group makes it impossible to say whether or not this difference was significant. It seems unlikely, considering the very large doses of ascorbic acid administered to both groups.

*Preoperative scorbutic diet and postoperative high vitamin C diet.* It seemed desirable to study the relative importance of the preoperative diet and the ascorbic acid intake in the postoperative interval, in determining the ascorbic acid content of the healing wound and other tissues at autopsy.

Contrasting experiments were planned, one group of animals receiving a scorbutic diet preoperatively

TABLE 6. Tensile Strength of Healing Wounds in Relation to Vitamin C Content.

	PRESSURE OF SKIN SEPARATION mm Hg	TENSILE OF WOUND FLTURE mm Hg	VITAMIN C CONTENT OF SCAR mg /100 gm
SCORBUTIC DIET		120	0.21
		80	0.47
		60	0.24
	Average	70	0.31
HIGH VITAMIN C DIET		300*	6.89
		160	7.74
		120	8.28
	Average	140	7.64

\*Wound failed to rupture at 300 mm Hg

and a high ascorbic acid intake postoperatively. The other group had a diet high in vitamin C

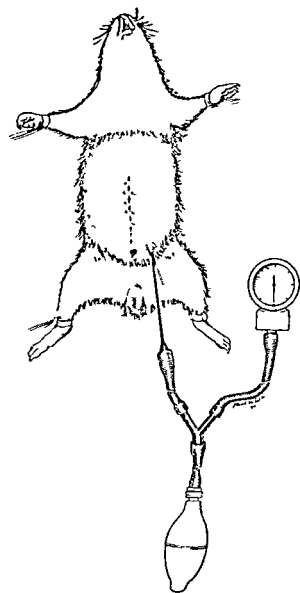


FIGURE 1. Method of Determining Tensile Strength of a Healing Wound in the Abdominal Wall of a Guinea Pig.

The peritoneal cavity is inflated until the wound ruptures; the pressure is recorded in millimeters of mercury.

preoperatively and a scorbutic diet postoperatively.

After two weeks on a scorbutic diet, 6 animals were subjected to operation. The operative procedure was the same as that performed in the

preceding groups of animals. Immediately after operation, a high ascorbic acid intake was insti-

As would be expected, the control biopsy showed a low concentration of ascorbic acid—the sam-

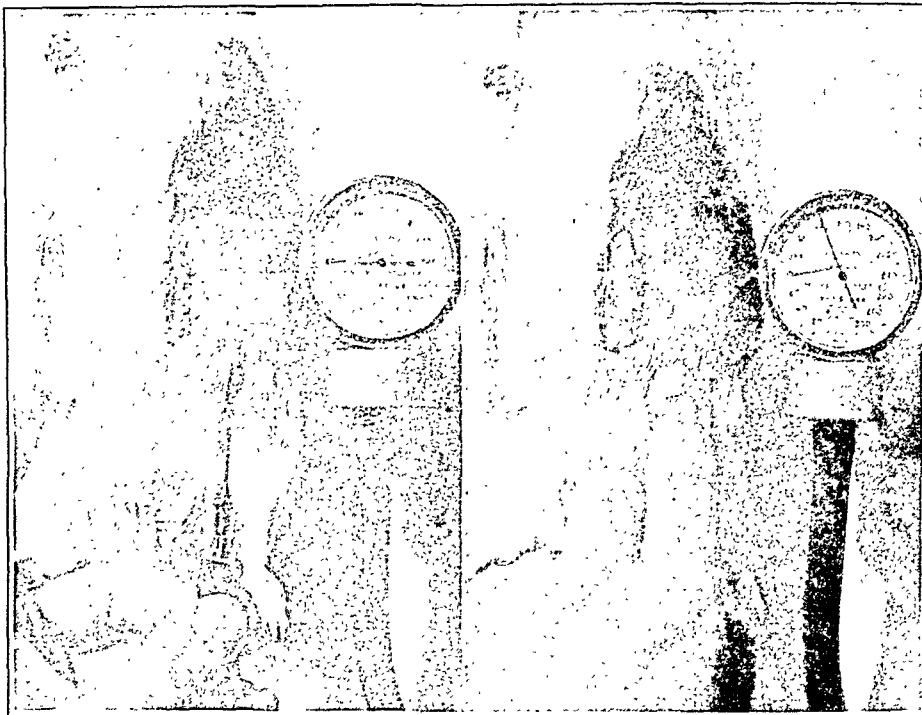


FIGURE 2.

*The photograph on the left shows the pressure required to separate the skin; that on the right, to rupture the wound.*

tuted, and at varying intervals the animals were killed and tissue assays for ascorbic acid done. The results appear in Table 4.

The variation of the postoperative intervals from

amount as that found for other animals on the same dietary regime (Table 2).

All the changes in tissue levels found at autopsy were similar to those found in animals maintained



FIGURE 3.

*The photograph on the left shows the pressure required to separate the skin; that on the right, to rupture the wound.*

four to fourteen days seemed to make no significant difference in the tissue levels at autopsy.

on a high ascorbic acid intake both preoperatively and postoperatively. The extent of the rise was

somewhat less in each tissue in the group under discussion.

**Preoperative high vitamin C diet and postoperative scorbutic diet.** In contrast with the above group, 4 animals were maintained on a high ascorbic acid intake for two weeks before operation, and on a scorbutic diet during the postoperative interval. The results of the ascorbic acid assays on the various tissues appear in Table 5.

Although these animals were saturated with large amounts of ascorbic acid before operation, the tissue levels obtained at autopsy were strikingly similar to those of the group of animals on a scorbutic diet both before and after operation. Why one animal failed to show any ascorbic acid in the control biopsy of the abdominal wall, in spite of the high intake of ascorbic acid preoperatively, is not clear.

**Tensile strength and ascorbic acid content of healing wounds.** The work of Lanman and Ingalls,<sup>1</sup> establishing the decrease in tensile strength of healing wounds in the presence of scurvy, has already been mentioned. We have attempted to repeat this experiment, correlating the tensile strength of the healing wound with the ascorbic acid content of the healing scar.

Three animals were established on a scorbutic diet. Abdominal incisions were made and sutured in the manner already described. The same diet as maintained postoperatively. Another group of 3 animals was given a diet high in ascorbic acid throughout the experiment, and the same operative procedure was carried out.

Since our previous studies had indicated that ascorbic acid content of the healing wound is certainly stabilized ten days after operation, animals were killed at this time, and the tensile strength of the healing scar in the abdominal wall was determined by a method similar to that used by Lanman and Ingalls. An ordinary, long gauge needle was introduced into the peritoneal cavity, and connected by rubber tubing to a rubber bulb and sphygmomanometer (Fig. 1). Air was introduced into the peritoneal cavity until a pressure was attained sufficient to cause rupture of the wound. The pressure, recorded in millimeters of mercury, was noted.

Characteristically, the wounds ruptured in two places. Skin separation occurred at first, followed by higher pressure by the rupture of the muscular layer.

The ruptured wounds were then excised and assayed for ascorbic acid content. The results of this experiment appear in Table 6. The average tensile strength in the animals on a high ascorbic acid intake was exactly twice that of the animals on a scorbutic diet, and the vitamin C content of the healing wounds showed the same striking contrast already noted (Tables 2 and 3).

Figure 2 shows a typical wound in a scorbutic animal at the moment of rupture. In Figure 3, the rupture of a wound in an animal on a diet rich in vitamin C is shown.

### SUMMARY AND CONCLUSIONS

Wide variations of the ascorbic acid content of guinea-pig tissues, as measured by Bessey's method of tissue assay, can be caused by a high or low intake of ascorbic acid.

Similar variations of ascorbic acid content can be demonstrated in a healing wound of the abdominal wall, depending on the vitamin C intake.

Animals on a scorbutic diet show essentially no increase in ascorbic acid in the healing area and slightly lowered values in the remainder of the abdominal wall, compared with the level in control biopsies obtained at the time of operation. The liver and kidney also show low levels.

On a high ascorbic acid intake, a striking increase in vitamin C content of the healing wound over that of the control biopsy can be demonstrated. The abdominal wall adjacent to the scar also shows a considerable rise, and a slight increase is found even at a distance from the wound. High levels are also found in the liver and kidney.

In these experimental animals, the tissue level attained by the preoperative administration of ascorbic acid is of much less importance in establishing the optimum ascorbic acid content of the healing wound and other tissues studied than the vitamin C intake during the postoperative period.

The tensile strength of wounds showing a high ascorbic acid content is much greater than that of those with low vitamin C values.

### REFERENCES

1. Lanman, T. H., and Ingalls, T. H. Vitamin C. Deficiency and wound healing: experimental and clinical study. *Ann. Surg.* 105: 616-625, 1937.
2. Taffel, M., and Harvey, S. C. Effect of absolute and partial vitamin C deficiency on healing of wounds. *Proc. Soc. Exper. Biol. & Med.* 38: 518-525, 1938.
3. Bessey, O. A. Method for the determination of small quantities of ascorbic acid and dehydroascorbic acid in turbid and colored solutions in the presence of other reducing substances. *J. Biol. Chem.* 126: 771-794, 1938.
4. McCullough, N. B. Vitamin C and resistance of guinea pig to infection with *Bacterium necrophorum*. *J. Infect. Dis.* 63: 34-53, 1938.
5. Zlatos, S. S. Vitamin C requirements of guinea pig. *Biochem. J.* 30: 1419-1429, 1936.
6. Eckert, E. E., and Pillemer, L. Vitamin C requirement of guinea pig. *Proc. Soc. Exper. Biol. & Med.* 44: 262, 1940.
7. Chevallier, A., and Choron, Y. Sur la teneur du cerveau et du foie en vitamine C chez le cobaye. *Compt. rend. Soc. de Biol.* 125: 65, 1937.
8. Giroud, A., Leblond, C. P., Batumamanga, R., and Goto, E. Le taux normal en acide ascorbique. *Bull. Soc. chim. Biol.* 20: 1088-1096, 1938.
9. Harris, L. J., Pasmore, R., and Vogel, W. Vitamin C and infection: influence of infection on the vitamin C content of the tissues of animals. *Lancet* 2: 183-186, 1937.
10. Lauber, H. J., and Rosenfeld, W. Histologische Untersuchungen über das Verhalten des Vitamins C in den verschiedenen Organen während der Wundheilung. *Klin. Wchnschr.* 17: 157-159, 1938.
11. Lyons, C. M., and King, C. G. Effect of diphenyl toxin on vitamin C content of guinea pig tissues. *J. Pharmacol. & Exper. Therap.* 56: 209-213, 1936.
12. Martini, E., and Tordy, C. Die Wirkung der hohen Temperatur auf den Ascorbinsäuregehalt der Meerschweinchenorgane. *Klin. Wchnschr.* 16: 1763, 1937.
13. Phillips, P. H., and Chang, C. Y. Influence of chronic fluorosis upon vitamin C in certain organs of the rat. *J. Biol. Chem.* 105: 405-419, 1935.
14. Polcand, A. V., and Ferrand, M. Über die Vergleichsbestimmung des Gehaltes an Ascorbinsäure in verschiedenen tierischen Organen. *Klin. Wchnschr.* 16: 1305-1310, 1937.
15. Svirlyte, J. L. Effect of diets and various substances on the vitamin C content of some organs of the rat. *Am. J. Physiol.* 116: 446-455, 1936.

## VITAMIN C AND WOUND HEALING\*

## II. Ascorbic Acid Content and Tensile Strength of Healing Wounds in Human Beings

MARSHALL K. BARTLETT, M.D.,† CHESTER M. JONES, M.D.,‡ AND ANNA E. RYAN, B.A.§

BOSTON

IN recent years, a considerable amount of evidence has established the efficacy of vitamin C in wound healing in animals. Lanman and Ingalls<sup>1</sup> first made direct measurements of the tensile strength of healing wounds in guinea pigs and found it decreased in the presence of scurvy. In the preceding paper,<sup>2</sup> we reported the results

a high ascorbic acid content was found to be much greater than that in those with low vitamin C values.

Elaborating on the work of Lanman and Ingalls, Taffel and Harvey<sup>3</sup> studied the effect of partial as well as absolute vitamin C deficiency on the tensile strength of healing wounds in guinea

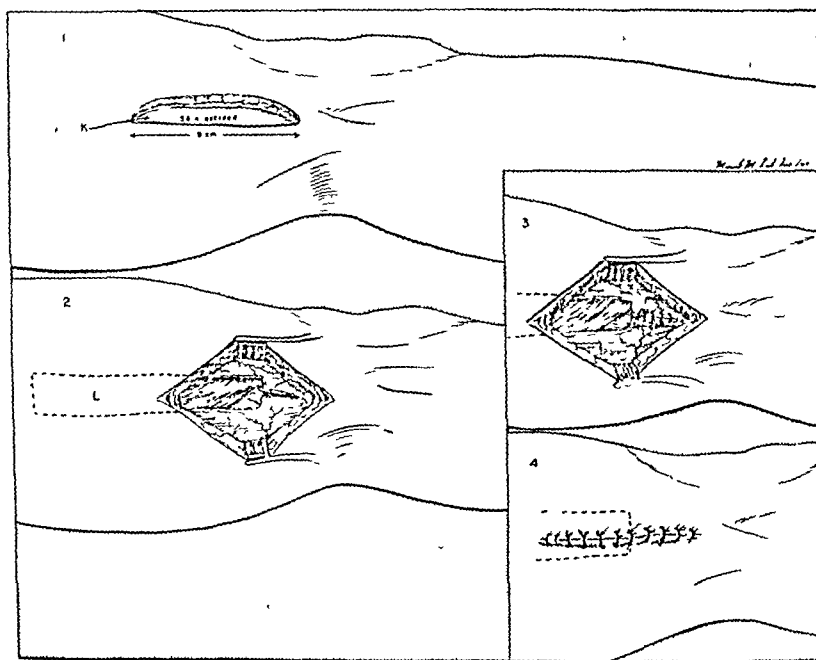


FIGURE 1. Method of Obtaining Tissue for Ascorbic Acid Assay and Tensile-Strength Determinations.

1—incision through skin and subcutaneous tissue with excision of a strip of skin for ascorbic acid assay (K); 2—fascia stripped out in the usual manner for repair of the hernia, and for ascorbic-acid assay (L), with an incision made in the fascia lata for 2 cm. distal to the area stripped out; 3—incision in fascia closed with fine silk sutures; 4—skin closed in the usual manner.

of studies on the tissue ascorbic acid content of similar wounds in guinea pigs and correlated this with the tensile strength of these wounds. A much higher concentration of vitamin C occurs in the wounds of animals on a high ascorbic acid intake than in those of animals on a scorbutic diet, and the tensile strength of wounds showing

pigs. There was a slightly greater tensile strength at four days after operation in animals with absolute scurvy than in the normal controls. At six days, the tensile strength was markedly inferior to that in normal animals. None of the scorbutic animals survived for a longer postoperative period. In their experiments, a state of partial scurvy was established as follows: after a week on the scorbutic diet supplemented by 5 mg. of ascorbic acid daily, all vitamin C was withheld for two weeks, and then 0.2 mg. of ascorbic acid was given on alter-

\*From the Medical and Surgical services, Massachusetts General Hospital.

†Assistant surgeon, Massachusetts General Hospital.

‡Clinical professor of medicine, Harvard Medical School, physician, Massachusetts General Hospital.

§Technician, Massachusetts General Hospital.

the days. Abdominal incisions were made after 30 days on this low vitamin C intake. It is extremely interesting that, although all the animals showed unmistakable gross evidence of scurvy at autopsy, tests for tensile strength on the healing wounds showed a significant decrease below that of normal controls only on the eighth and tenth days after operation. Tests on the fourth and sixth days showed no appreciable variation from the controls, and those on the twelfth and fourteenth days again approached normal.

The effect of prolonged reduced intake of vitamin C on wound healing in an otherwise normal adult human subject has been studied by Cranston, Lund and Dill<sup>4</sup> and by Hunt.<sup>5</sup> In both studies, the histologic appearance of the wound

the same patient, followed by the administration of large doses of ascorbic acid, showed no macroscopic or microscopic difference from the first wound.

The present studies were undertaken in an attempt to obtain further information regarding the value of vitamin C in wound healing in human beings, by means of direct observations on the tensile strength of healing wounds and a correlation of these with the tissue content of ascorbic acid and plasma ascorbic acid levels.

#### METHODS

Male patients admitted to the hospital for the repair of inguinal hernias who were good surgical risks and on whom the use of fascia lata in

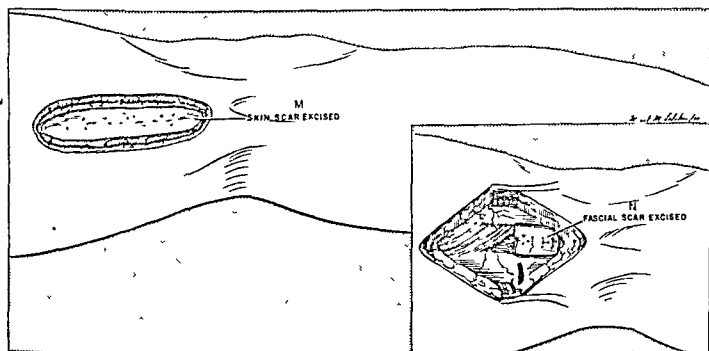


FIGURE 2. Method of Subsequently Obtaining Tissue for Ascorbic Acid Assay and Tensile-Strength Determinations.

*The skin scar is excised (M), exposing the healing fascial scar (N), which is also excised. The skin is then closed in the usual manner.*

was used as an index of abnormal healing. Cranston, Lund and Dill found that adequate wound healing occurred after the plasma ascorbic acid had been zero for forty-four days and when the white-cell and platelet ascorbic acid level was 4 mg. per 100 cc. A second wound, made when the plasma ascorbic acid had been zero for one hundred and forty-one days and the white-cell and platelet ascorbic acid content had been at zero for sixty-one days, failed to heal in a normal manner after ten days, and showed lack of intercellular substance and capillary formation on histologic examination. The intravenous administration of 1000 mg. of ascorbic acid daily for ten days brought about microscopic evidence of good healing. Hunt<sup>5</sup> reported histologic evidence of healing of an experimental wound in a subject who had been on a reduced vitamin C intake for three months and who had a blood ascorbic acid content of 0.34 mg. per 100 cc. A second experimental wound in

the repair was contemplated were selected for these studies.

During the preliminary period of two to four days, the plasma ascorbic acid was determined by the method of Mindlin and Butler,<sup>6</sup> and the daily urinary output measured by Bessey's<sup>7</sup> method. Throughout the hospital stay, these patients were maintained on a diet containing 100 mg. of vitamin C daily. Supplementary ascorbic acid was given to some patients before and after operation, as described in the case reports.

Studies were carried out on a total of 6 patients. Of these, 5 had unilateral hernias, and 1 had bilateral hernias.

The operations were performed under spinal anesthesia, and the usual hernia repair was done. Fascia lata was obtained through a longitudinal skin incision about 8 cm. in length just above the knee on the lateral aspect of the thigh. A strip of skin, weighing about 2 gm., was excised

from the edge of this wound for ascorbic acid assay as a control biopsy. The fascia was removed by means of a stripper, and in addition to that necessary for the hernia repair, enough was removed for ascorbic acid assay. The tissue ascorbic acid content was determined on the ex-

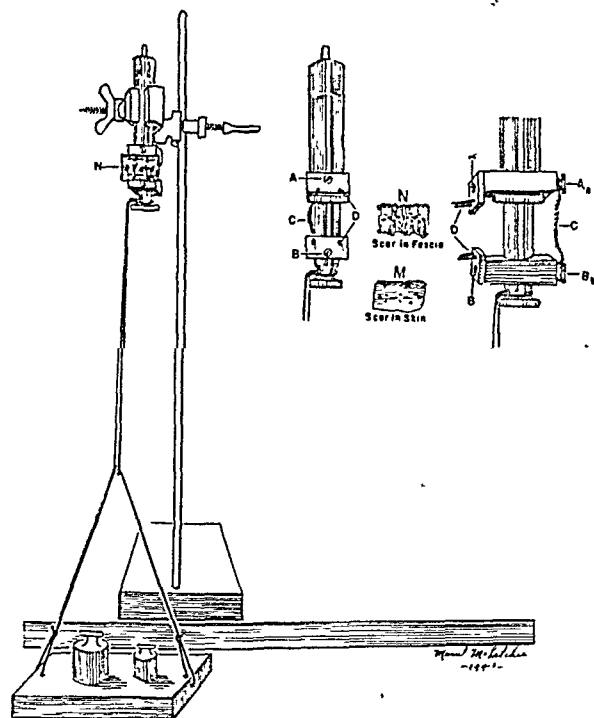


FIGURE 3. Method for Determining the Tensile Strength of Healing Scars in Skin and Fascia.

The apparatus consists of a 5-cc. glass syringe, with collars mounted on the barrel and plunger (Aa and Bb). On each collar a bar is attached, pivoted at its center (A and B). Two pins (D), spaced 1 cm. apart, are mounted on each bar, and the tissue to be tested (M or N) is placed on these four pins. Tension is applied by weights on the platform. The pull necessary to rupture the scar is recorded in grams.

cised skin and fascia by the method described by Bessey<sup>7</sup> and previously employed in our animal experiments. Distal to the area of excised fascia, a longitudinal incision 2 cm. in length was made in the fascia lata, parallel to its fibers, and this was closed with interrupted sutures of fine silk. The skin was then closed in the usual manner with interrupted silk (Fig. 1).

The wound was allowed to heal for ten days, the skin sutures being removed on the eighth day. At the end of ten days, under novocain block anesthesia, the skin incision in the thigh was excised with a margin of slightly less than 1 cm. of skin on each side of the scar; the incision in the fascia was excised with the same margin of tissue (Fig. 2).

The tensile strength of the healing wound and the tissue ascorbic acid content were determined on the skin and fascia. In some cases, enough

skin was available to allow duplicate determinations. The tensile strength was measured by the application of a direct pull on the healing scar, as illustrated in Figure 3. The apparatus consisted of a 5-cc. glass syringe, with collars mounted on the barrel and plunger. Each collar carried a bar, pivoted at the center, bearing two pins spaced 1 cm. apart. The pivot provided an equalized pull on the tissue mounted on the pins, when tension was applied by means of weights placed on the platform.

As a result of duplicate determinations on portions of the same skin scars, it became evident that there was considerable variation by this method, and we believe that only gross differences should be considered significant.

### CASE REPORTS

CASE 1. A. A., a 65-year-old man, was admitted for repair of a right inguinal hernia. The plasma ascorbic acid was 0.60 and 0.66 mg. per 100 cc. on two occasions be-

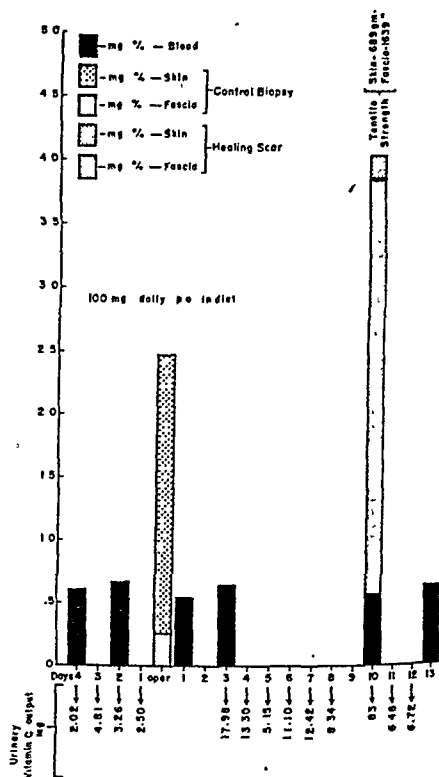


FIGURE 4. Case 1.

Determinations of ascorbic acid in the blood plasma, in control biopsies of skin and fascia and in healing skin and fascial scars are shown. Urinary excretion of vitamin C is recorded in twenty-four-hour amounts, and the tensile strengths of the skin and fascial scars are listed. Where columns are superimposed, the actual amount of each component is the maximum height of the column above the abscissa.

fore operation, and no significant variation from this level occurred following operation.

Control biopsies of skin and fascia from the left leg were obtained at the time of herniorrhaphy. The skin

showed an ascorbic acid content of 2.49 mg, and the fascia one of 0.29 mg per 100 gm. At the end of 10 days, the skin and fascia scars were excised. The skin showed a tensile strength of 700 gm and a vitamin C content of 404 mg per 100 gm. The fascia scar broke at a tension of 1600 gm and contained 388 mg of ascorbic acid per 100 gm. The complete data on this patient appear in Figure 4.

CASE 2 E J L, a 36-year-old man, was admitted for repair of a left inguinal hernia. The preoperative plasma ascorbic acid was 0.20 mg per 100 cc on two occasions. Control biopsies of skin and fascia lata showed a vitamin C

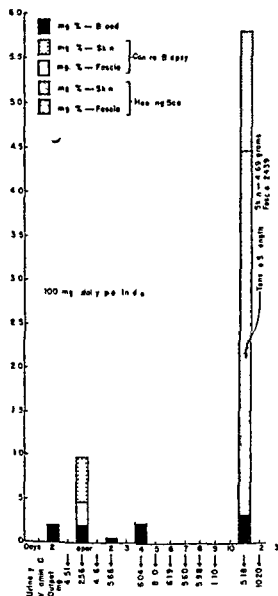


FIGURE 5 Case 2

content of 0.99 mg and 0.48 mg per 100 gm, respectively. After healing for 10 days, the skin scar had a tensile strength of 4200 gm and an ascorbic acid content of 5.92 mg per 100 gm. The fascia scar ruptured at 1400 gm with a vitamin C content of 4.48 mg per 100 gm.

In this patient, except for a transient drop after operation the plasma ascorbic acid showed no significant variation during the postoperative interval. This transient fall has been previously noted by various workers. The studies on this patient are shown in Figure 5.

CASE 3 J S, a 24-year-old man, entered the hospital because of a left inguinal hernia. Two preoperative plasma ascorbic acid determinations showed 0.31 and 0.26 mg per 100 cc. Control biopsies of the skin and fascia lata were taken. The skin contained 0.84 mg and the fascia 0.11 mg of ascorbic acid per 100 gm. From the day of operation, 1000 mg of vitamin C was given daily in addition to the 100 mg contained in the regular diet. The plasma ascorbic acid level rose promptly and remained between 0.68 and 1.01 mg per 100 cc during the postoperative interval. A corresponding rise in urinary output of vitamin C occurred.

After healing for 10 days, the skin and fascia scars were excised from the leg. The skin scar had a tensile strength of 1500 gm and an ascorbic acid content of 5.23 mg per 100 gm. The healing fascia broke under a tension of 1200 gm, with a vitamin C tissue level of 7.65 mg per 100 gm. The complete data on this patient appear in Figure 6.

CASE 4 F W, a 62-year-old man, proved to be the most interesting patient studied. He had bilateral inguinal hernias, which were repaired separately. He also had the lowest preoperative plasma ascorbic acid level in the group—0.09 and 0.08 mg per 100 cc on two determinations. There was no clinical evidence of scurvy.

At the first operation the right hernia was repaired, and control biopsies of skin and fascia were obtained from the left leg. These tissues both showed a tissue ascorbic acid level of zero. No ascorbic acid, other than the 100 mg daily in the diet was given after operation, and the plasma ascorbic acid remained at the same low level.

At the end of 10 days, the left hernia was repaired, fascia from the right leg being used, and control specimens of skin and fascia were obtained from the new incision. They also showed a zero level of ascorbic acid. At the same

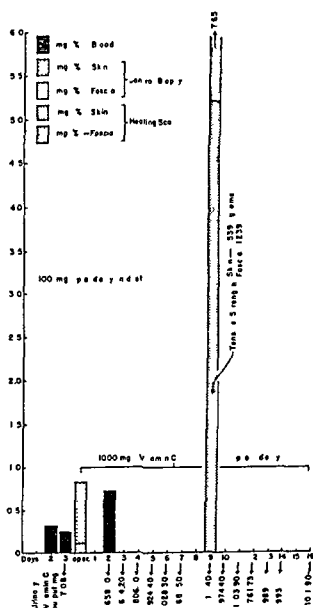


FIGURE 6 Case 3

time the 10-day-old scars in the skin and fascia of the left leg were excised. The skin scar had a vitamin C level of 0.67 mg per 100 gm and a tensile strength of 400 gm (average of two determinations). The healing fascia had a tissue level of ascorbic acid of zero and ruptured at a tension of 300 gm.

The patient was then given 1000 mg of ascorbic acid by mouth daily, in addition to that in the regular diet, and the blood ascorbic acid promptly rose to above 1.0 mg per 100 cc and remained at this level, with a corresponding increase in the urinary output of ascorbic acid.



Ten days after the second operation, the healing skin and fascia scars were excised from the right leg. An ascorbic acid assay on the skin gave a result of 6.77 mg.

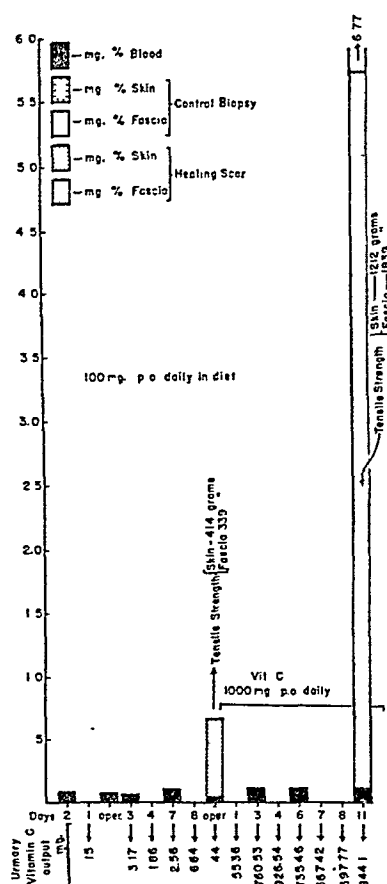


FIGURE 7. Case 4.

*Tissue assay of vitamin C on the control biopsies of the skin and fascia at both operations and of the healing fascia excised at the second operation were all zero, and so do not appear.*

per 100 gm., and the scar separated with a pull of 1200 gm. (average of three determinations). The fascia contained 5.73 mg. of vitamin C per 100 gm., and the scar had a tensile strength of 1800 gm. Figure 7 shows the results of these studies in graphic form.

**CASE 5.** A.D., a 26-year-old man, was recommended for admission to the hospital because of a left inguinal hernia. The plasma ascorbic acid was found to be 0.26 mg. per 100 cc., and he was given 200 mg. of vitamin C daily for 2 weeks prior to admission. After a week, the plasma ascorbic acid was 0.98 mg. per 100 cc., and on admission it was 0.81 mg. The patient was given the same dose (200 mg.) of ascorbic acid daily in addition to 100 mg. in the diet, and on the day of operation the plasma ascorbic acid was 0.87 mg. per 100 cc. The hernia was repaired, and skin and fascia were obtained from the right leg for vitamin C assay. The skin contained 0.78 mg. and the fascia 0.17 mg. of ascorbic acid per 100 gm.

Except for the day of operation, when no ascorbic acid was given, the daily intake was maintained at a total of 300 mg. of vitamin C daily. Ten days after operation, the healing skin and fascia scars were excised from the leg. In addition, a small pigmented nevus was removed

from the back, together with a margin of surrounding normal skin.

The healing skin showed 5.54 mg. of ascorbic acid per 100 gm., and the scar ruptured with a pull of 600 gm. (average of three determinations). The fascia had a vitamin C level of 7.24 mg. per 100 gm. and a tensile strength of 1100 gm. The pigmented nevus was discarded, and the surrounding skin was assayed for vitamin C. A level of 1.88 mg. per 100 gm. was obtained. These studies appear in Figure 8.

**CASE 6.** T.D., a 48-year-old man, was admitted to the hospital because of a large left inguinal hernia. A plasma ascorbic acid determination 2 weeks before admission showed a level of 0.73 mg. per 100 cc. The patient was given 600 mg. of vitamin C daily, and this was continued, together with the 100 mg. in the regular diet, until 10 days after operation, except for the day of operation, when he received none. The plasma ascorbic acid was 1.26 mg. per 100 cc. on admission, and except for a transient

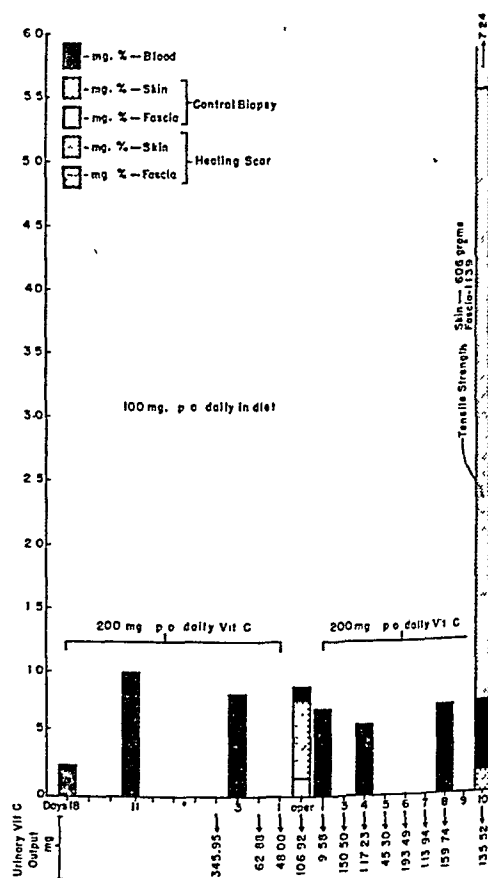


FIGURE 8. Case 5.

drop after operation, it remained above 1.0 mg. per 100 cc. until the supplementary dose of vitamin C was withdrawn.

At operation, the hernia was repaired with fascia from the right thigh, and control biopsies of the skin and fascia lata were obtained. The skin contained 1.63 mg. and the fascia 0.20 mg. of ascorbic acid per 100 gm.

After 10 days, the healing skin and fascia scars were excised from the leg. A pigmented nevus on the same leg, but at some distance from the healing area, was also excised, with a margin of normal skin. The healing skin

had an ascorbic acid content of 4.64 mg. per 100 gm., and the scar ruptured at a tension of 1600 gm. (average of four determinations). The fascia scar contained 6.79 mg of ascorbic acid per 100 gm. and had a tensile strength of 1700 gm. The skin surrounding the small pigmented nevus showed a vitamin C level of 1.10 mg. per 100 gm. These results appear in Figure 9.

### DISCUSSION

We have attempted to obtain information concerning the importance of vitamin C in wound healing in human beings by means of tissue ascorbic

comparable rise in ascorbic acid content and tensile strength is shown in spite of the variation in the preoperative plasma ascorbic acid from 0.20 to 1.19 mg. per 100 cc. In fact, in these 5 cases, the highest apparent tensile strength (2400 gm.) was found in the patient with the lowest preoperative plasma ascorbic acid (0.20 mg. per 100 cc.).

Except for Case 4, the ascorbic acid contents of the control biopsies of fascia were fairly consistent, varying from 0.11 to 0.48 mg. per 100 gm., with an average of 0.25 mg. Incidentally, this was considerably lower than the average vitamin C content of the control skin biopsies in these same patients, which was 1.35 mg. per 100 gm.

The healing fascia scar showed a marked rise in ascorbic acid content in every case, ranging from 3.88 to 7.65 mg. per 100 gm., with an aver-

TABLE 1. Studies on Healing of Human Fascia.

Case No	PRE- OPERATIVE PLASMA ASCORBIC ACID	CONTROL BIOPSY TISSUE ASCORBIC ACID	TEN DAY OLD SCAR TISSUE ASCORBIC ACID	TENSILE STRENGTH
	mg /100 cc	mg /100 gm	mg /100 gm.	gm
1	0.63	0.29	3.88	1600
2	0.20	0.48	4.48	2400
3	0.29	0.11	7.65	1200
5	0.64	0.17	7.24	1100
6	1.19	0.20	6.79	1700
Average	0.63	0.25	6.01	1600
4 (first operation)	0.09	0.0	0.0	300
(second operation)	0.07	0.0	5.73	1800

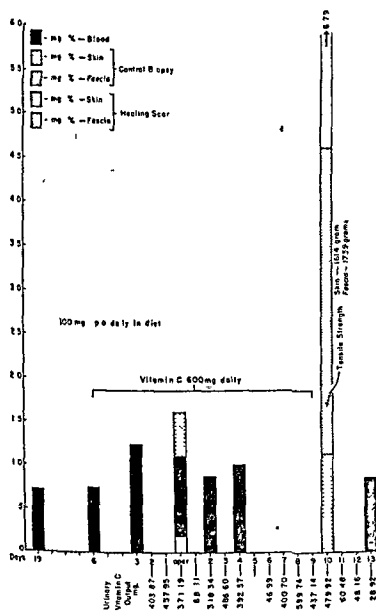


FIGURE 9. Case 6.

acid determinations, contrasting the vitamin C content of ten-day-old healing scars in fascia and skin with that of control biopsies of these tissues obtained at the time the incisions were made. Direct tensile-strength determinations were also made on the healing fascia and skin scars.

In the healing of an ordinary abdominal wound, the strength of the fascia layer is of primary value, and we are particularly interested in the results of the determinations on this tissue. These data have been assembled for convenient study in Table 1.

With the exception of Case 4, we believe that there is no significant variation in the behavior of the healing fascia in the cases reported. A

age value of 6.01 mg. This is an average rise of more than twenty-four times the control level.

The tensile strengths of these five specimens of fascia varied from 1100 to 2400 gm., and averaged 1600 gm.

We believe that the values obtained on these 5 patients can be considered normal, and in this group, even a plasma ascorbic acid level as low as 0.2 mg. per 100 cc. did not cause a significant variation from the normal in vitamin C content or tensile strength of the healing fascia.

Case 4 offers a contrasting picture, which we regard as significant, because the plasma ascorbic acid was very low preoperatively (0.08 and 0.09 mg. per 100 cc. on two determinations), and because the presence of bilateral inguinal hernias offered the opportunity for contrasting experiments in the same patient. The first leg wound was allowed to heal without vitamin C therapy, other than the 100-mg. daily dose provided in the regular diet. During the ten-day healing period of the second leg wound, this dietary intake was supplemented by 100 mg. of ascorbic acid daily given by mouth. The tissue ascorbic acid level of the control biopsy of fascia taken at the time of the first operation was zero. During the ten-day healing period of this wound, the low plasma as-

corbic acid level remained unchanged, and at the end of this time the excised fascia scar still showed an ascorbic acid value of zero and a tensile strength of only 300 gm., or about one fifth of normal (1600 gm.). The control biopsy of fascia from the second leg wound also showed a zero value for ascorbic acid. This wound was allowed to heal for ten days, 1000 mg. of ascorbic acid being given orally each day in addition to the regular diet. The plasma ascorbic acid promptly rose to over 1.0 mg. per 100 cc. At the end of ten days, the healing fascia scar was excised. Its ascorbic acid content was 5.73 mg. per 100 gm., which is slightly lower than the average of 6.01 mg. per 100 gm. noted in the other cases. The tensile strength of this fascia scar was 1800 gm., a figure slightly higher than the average of 1600 gm., for the other cases, and six times as high as that (300 gm.) for the scar in the wound in the other leg, which healed without benefit of vitamin C therapy.

The results of the studies of vitamin C content and tensile strength of skin healing appear in Table 2. These figures followed essentially the

TABLE 2. *Studies on Healing of Human Skin.*

CASE NO	PRE- OPERATIVE PLASMA ASCORBIC ACID	CONTROL BIOPSY TISSUE ASCORBIC ACID	TEN-DAY TISSUE ASCOR- BIG ACID	OLD SCAR TENSILE STRENGTH
	mg /100 cc.	mg /100 gm.	mg /100 gm.	gm
1	0.63	2.49	4.04	700
2	0.20	0.99	5.82	4200
3	0.29	0.84	5.23	1500
5	0.84	0.78	5.54	600
6	1.19	1.63	4.64	1600
Average	0.63	1.35	5.05	1700
4 (first operation)	0.09	0.0	0.67	400
(second operation)	0.07	0.0	6.77	1200

same pattern as those on the healing fascial scars, although there was much more variation in the tensile-strength determinations.

If we exclude Case 4 and accept the averages of the other 5 cases as normal values, we find an ascorbic acid content of the control skin biopsy of 1.35 mg. per 100 gm., which rose to 5.05 mg. in the ten-day-old scar. The average tensile strength of these scars was 1700 gm.

Case 4 showed an ascorbic acid level of zero in the control specimen of skin, which rose only to 0.67 mg. per 100 gm. after ten days of healing without vitamin C therapy other than the 100 mg. daily in the diet. The tensile strength of this scar was 400 gm., one quarter of the normal value. The second leg wound showed no vitamin C in the control skin biopsy. After ten days of intensive vitamin C therapy, the scar had an ascorbic acid content of 6.77 mg. per 100 gm., which is

somewhat higher than the normal (5.05 mg.) Its tensile strength was 1200 gm., as against 400 gm. for the untreated scar in the same patient, and 1700 gm. for the average of the other cases.

We believe that Case 4 demonstrates conclusively two important points: that a sufficient depletion of vitamin C, reflected in a very low plasma ascorbic acid, interferes with normal wound healing, as measured by tissue ascorbic acid content and tensile strength; and that, in spite of a very low plasma ascorbic acid at the time of operation, normal wound healing can be brought about by adequate vitamin C therapy during the healing period.

There seems to be no evidence from these studies that a plasma ascorbic acid level of 0.20 mg. per 100 cc. indicates a sufficient depletion of vitamin C to interfere with normal wound healing, and this suggests that the generally accepted concept that plasma ascorbic acid levels below 0.50 mg. per 100 cc. indicate significant vitamin C depletion must be revised downward.

It was found in our work on guinea pigs that, with an adequate vitamin C intake, not only the tissues of the healing wound show a higher level of ascorbic acid than the control biopsy, but a similar though smaller rise is found in the abdominal wall at some distance from the wound. In 2 patients (Cases 5 and 6), specimens of skin were obtained at a distance from the healing wound at the time that the wound biopsy was done. As shown in Figures 8 and 9, one of these specimens showed a level of 1.88 mg. per 100 gm. in contrast to an original value of 0.78 mg. in the control biopsy, whereas the other showed a decrease from 1.63 mg. in the control biopsy to 1.10 mg. per 100 gm., in the normal skin excised ten days later.

### CONCLUSIONS

A sufficient depletion of vitamin C produces a decreased ascorbic acid content and tensile strength in healing wounds in the skin and fascia of human beings.

A fasting plasma ascorbic acid level below 0.20 mg. per 100 cc. must be reached before these changes appear.

In the presence of adequate vitamin C, the magnitude of the rise in ascorbic acid content in healing fascial scars, compared with that of control biopsies, is much greater than that shown by healing skin scars.

In spite of a low plasma ascorbic acid level at the time of operation, normal wound healing may be produced by adequate vitamin C therapy during the postoperative period.

## REFERENCES

- 1 Lerman T. H. and Ingalls T. H. Vitamin C deficiency and wound healing: experimental and clinical study. *Ann Surg* 105 616 625 1937.
- 2 Flett M. K., Jones C. M. and Ryan A. E. Vitamin C and wound healing. I. Experimental wounds in guinea pigs. *New Eng J Med* 226 469 473 1941.
- 3 Taffel M. and Harvey S. C. Effect of absolute and partial vitamin C deficiency on healing of wounds. *Proc Soc Exper Biol & Med* 38 518-525 1938.
- 4 Crandon J. H., Lund C. G. and Dill D. B. Experimental human scurvy. *New Eng J Med* 223 353 369 1940.
- 5 Hirst A. H. Role of vitamin C in wound healing. *Brit J Surg* 28 436 461 1941.
- 6 Mandl R. I. and Blier A. M. Determination of ascorbic acid in plasma: a microtiter and microchemical method. *J Biol Chem* 122 63 68 1938.
- 7 Beatty O. A. Method for the determination of small quantities of ascorbic acid and dehydroascorbic acid in turbid and colored solutions in the presence of other reducing substances. *J Biol Chem* 176 1 84 1946.

## THE SO-CALLED "COAGULATION DEFECT" IN MENSTRUAL BLOOD\*

EUGENE L. LOZNER, MD,<sup>1</sup> ZILFEN TAYLOR, MD,<sup>2</sup> AND F. H. L. TAYLOR, PhD<sup>3</sup>  
(with the technical assistance of M. A. Adams and Harriet MacDonald)

BOSTON

THE fluidity of menstrual blood and its apparent failure to clot have been the subject of numerous investigations.<sup>1-3</sup> Although all observers agree on the existence of the phenomenon there is little agreement concerning its cause. It has been with equal enthusiasm ascribed to an anticoagulant present in uterine cervical or vaginal secretions, to the removal or absence of one or more of the factors concerned with blood coagulation and to changes in the circulating blood. The existence of this form of incoagulable blood is of interest to the investigators of blood coagulation, since it represents a phenomenon that might possibly be explained in the light of the newer knowledge of the blood coagulation reaction.

From a consideration of the theory of blood coagulation at present accepted in the United States, it appears that incoagulable blood may result from a deficiency of one or more of the plasma constituents concerned with coagulation,—calcium, prothrombin and fibrinogen,—or in a lack of the clot promoting activity associated with the euglobulin fraction of plasma, which has been found to be markedly reduced in the blood of patients with hemophilia.<sup>4</sup> Incoagulability of menstrual blood might also result from the presence of some specific anticoagulant. This communication presents the results of investigations undertaken to determine which of these various factors are concerned with fluidity of menstrual blood.

## METHODS

At the suggestion of Dr. George Van S. Smith, of the Fearing Research Laboratory, Free Hospital for Women, the collection of menstrual blood was made by the insertion of a rubber cup,<sup>5</sup> which acted as an occlusive pessary, high in the vagina. Collections were usually made for twelve hour periods, after which the contents of the cups were transferred to blood bottles, examined for the presence of clots, and placed in a refrigerator. For certain purposes, collections were made occasionally for shorter periods. Ten samples of menstrual blood were collected in this manner from 5 healthy women.

The methods for studying the effect of menstrual blood on normal human and hemophilic blood were those previously described from this laboratory. The rabbit brain thromboplastin used in the investigation was prepared by our modification of the method of Quick.<sup>6</sup> Thrombin was obtained from prothrombin, prepared by the method of Seegers et al.,<sup>6</sup> by the action of rabbit brain thromboplastin.

For control experiments against menstrual blood, two well known laboratory forms of incoagulable blood were used: citrated and defibrinated blood. In the experimental work reported below, the observations were carried out on the supernatant fluids after centrifuging, at 1500 r.p.m. for ten minutes, samples of citrated, defibrinated and menstrual blood. All observations were made in a constant temperature water bath at 37.5°C. For the sake of brevity, one typical experiment on each phase of the investigation is given. The results in all were entirely similar.

## EXPERIMENTAL RESULTS

The presence of an anticoagulant in menstrual blood was investigated by the placing of 0.1 cc

\*Presented in part before the American Federation for Clinical Research, Atlantic City, New Jersey, May 5, 1941.  
From the Third Medical Laboratory, Second and Fourth Medical Services (Harvard) Boston City Hospital, the Department of Medicine, Harvard Medical School and the New England Hospital for Women and Children.  
This study was aided in part by a grant in recognition of Dr. Francis W. Peabody's services to the Foundation from the Ella S. and Philip S. Foundation.  
<sup>1</sup> Assistant in Medicine, Harvard Medical School, resident physician at Third Medical Laboratory, Boston City Hospital.  
<sup>2</sup> Visiting physician, New England Hospital for Women and Children.  
<sup>3</sup> The research associate in medicine, Harvard Medical School, chemist, Thorndike Memorial Laboratory, Boston City Hospital.

\*Commercially marketed under the trade name Hypon.

of citrated, defibrinated and menstrual bloods in glass tubes and the addition of 2 cc. of fresh uncoagulated normal venous blood to each, with a proper control. Table 1 shows conclusively that no

TABLE 1. *The Effect of Samples of Citrated, Defibrinated and Menstrual Blood on the Coagulation Time of Normal Venous Blood.*

PREPARATION ADDED	COAGULATION TIME min.
None (control)	7
Citrated blood	7
Defibrinated blood	2
Menstrual blood	3

prolongation of the coagulation time of normal blood occurred as a result of the addition of any of the three preparations. With menstrual and defibrinated blood, there was indeed a shortening of the coagulation time of the normal blood. This indicates the presence of clot-promoting activity rather than that of an anticoagulant.

These observations were repeated, hemophilic blood being used in place of normal blood. The results are shown in Table 2. It will be observed

TABLE 2. *The Effect of Samples of Citrated, Defibrinated and Menstrual Blood on the Coagulation Time of Hemophilic Venous Blood.*

PREPARATION ADDED	COAGULATION TIME min.
None (control)	69
Citrated blood	12
Defibrinated blood	7
Menstrual blood	3

that again there was no prolongation, but a sharp diminution, of the coagulation time of the hemophilic blood. Menstrual blood has therefore an abundance of clot-promoting factor for hemophilic blood. Such an activity has been described as occurring in normal, cell-free, citrated plasma.<sup>4</sup> The data show that menstrual blood contains even more of this factor than citrated normal blood.

Since the presence of an anticoagulant could not be demonstrated in any of the samples of menstrual blood, observations were directed toward an attempt to discover whether one or more of the factors concerned in the blood-coagulation reaction were diminished or absent.

Total calcium determinations on menstrual blood were always within the normal limits obtaining for circulating venous blood. The data of Tables 1 and 2 indicate quite clearly that menstrual blood also contains sufficient clot-promoting activity to initiate blood coagulation in both normal and hemophilic blood. However, to establish beyond question that the fluidity of menstrual blood was not due to deficiency either of calcium

or of thromboplastin, 0.1-cc. amounts of a solution containing 0.25 per cent calcium chloride, with and without the addition of a 0.1-cc. solution of rabbit-brain thromboplastin, were added to 0.1-cc. samples of citrated, of defibrinated and of menstrual blood in considerable excess (Table 3). It is evident that the addition of neither calcium nor both calcium and rabbit-brain thromboplastin caused clotting of the menstrual blood. In this respect, the menstrual blood resembled defibrinated blood. Following the addition of calcium and rabbit-brain thromboplastin to citrated blood, coagulation occurred in the normal time of twenty-

TABLE 3. *The Effect of Calcium Chloride and of Calcium and Thromboplastin Solutions on Samples of Citrated, Defibrinated and Menstrual Blood.*

TYPE OF BLOOD	SOLUTION ADDED	COAGULATION TIME sec
Citrated	Calcium chloride	120
Defibrinated	Calcium chloride	No clot
Menstrual	Calcium chloride	No clot
Citrated	Calcium chloride and thromboplastin	25
Defibrinated	Calcium chloride and thromboplastin	No clot
Menstrual	Calcium chloride and thromboplastin	No clot

five seconds. By exclusion, a deficiency or absence of prothrombin or fibrinogen, or both, appears to be the cause of the fluidity of menstrual blood. This hypothesis was investigated by efforts to demonstrate fibrinogen in the menstrual fluid and, as shown below, by the addition of prothrombin and fibrinogen to the menstrual blood. The presence of fibrinogen could not be demonstrated in menstrual blood by any of the standard chemical procedures.

Table 4 shows that the addition of 0.1 cc. of thrombin to 0.1-cc. samples of menstrual and of

TABLE 4. *The Effect of Thrombin, Fibrinogen, and Prothrombin and Fibrinogen Solutions on Samples of Citrated, Defibrinated and Menstrual Blood.*

TYPE OF BLOOD	SOLUTION ADDED	COAGULATION TIME sec
Citrated	Thrombin	3
Defibrinated	Thrombin	No clot
Menstrual	Thrombin	No clot
Citrated	Fibrinogen	No clot
Defibrinated	Fibrinogen	No clot
Menstrual	Fibrinogen	No clot
Citrated	Prothrombin and fibrinogen	360
Defibrinated	Prothrombin and fibrinogen	60
Menstrual	Prothrombin and fibrinogen	71

defibrinated blood preparation caused no coagulation. This indicated conclusively the absence of fibrinogen. However, the restoration of 0.1 cc. of fibrinogen alone was unsuccessful in causing 0.1-cc. samples of menstrual blood and of defibrinated blood to clot. No effect was expected with citrated blood, since a full quota of fibrinogen was

present, as shown by clotting following the addition of thrombin. When, however, a mixture containing 0.1-cc. each of fibrinogen and prothrombin was added to 0.1-cc. samples of menstrual blood and of defibrinated blood, clotting occurred abruptly. The presence of the increased titer of clot-promoting substance in both menstrual and defibrinated blood caused the coagulation time, when excess fibrinogen and prothrombin were added, to fall below that of citrated blood.

### DISCUSSION

In their behavior toward thrombin, prothrombin and fibrinogen, the menstrual blood and the defibrinated blood, or serum, were strikingly similar. The observations indicate that the fluidity of menstrual blood is caused by the absence of both prothrombin and fibrinogen. Expressed in common language, it follows that menstrual fluid is blood that has already clotted, and that there is no "coagulation defect." Hence, menstrual blood is serum containing formed elements and epithelial debris.

A natural question arises. If menstrual blood has already clotted, where are the clots? It must be remembered that menstrual blood is slowly excreted and that much of the fibrin formed has had time to be subjected to lytic action. Only two of the samples of menstrual blood, however, showed any increased fibrinolytic power. The non-protein nitrogen of menstrual blood was also not increased. Furthermore, it is known that the presence of small clots in normal menstrual exudates is common.<sup>7-9</sup> When menstrual flow is copious or abnormally increased,—that is, when there is a faster flow,—the presence of large clots is a characteristic finding. Examination of the menstrual-blood samples used in this investigation showed macroscopic clots in 3 cases.

One clinical application of these observations lies in the interdiction, by some surgeons, of operations during the menstrual period. We have been unable to demonstrate any change in the coagulability of the circulating blood during the men-

strual period. This, together with the findings recorded, indicates that the fluidity of menstrual blood alone does not constitute a reasonable basis for postponing surgical operations to the intermenstrual period. However, patients who suffer from a true hemorrhagic diathesis during the menstrual period have been reported. In these rare cases, when the platelet count is low, operations should of course be deferred until this condition is remedied or absent.

It is interesting that Hippocrates<sup>10</sup> made studies on the menstrual blood of women three thousand years ago. He observed:

The menstrual blood is thicker, redder, and flows more copiously about the middle period of the discharge than either at its commencement or termination. Its amount in health is about twenty ounces in two or three days,—the usual period,—although great diversity exists in this respect, depending on the constitution of the individual. *The blood which is discharged, is red like that of victims, and it coagulates promptly if the woman is in health [italics ours].*

### CONCLUSIONS

From the evidence presented, it is apparent that menstrual blood is blood that has already clotted. There is therefore no true "coagulation defect," and menstrual blood is a suspension of the formed elements of blood and tissue debris in serum.

### REFERENCES

- 1 Bell, W. B. The causes of the non coagulability of normal menstrual blood and of pathological clotting. *J. Path. & Bact.* 18:462-468, 1913.
- 2 Novak, E., and TeLinde, R. W. Endometrium of the menstruating uterus. *J. A. M. A.* 83:900-906, 1925.
- 3 King, J. L. A study of the anticoagulating substances in the mucous membrane of the uterus. *Am. J. Physiol.* 57:444-453, 1921.
- 4 Patek, A. J., and Taylor, F. H. L. Hemophilia. II. Some properties of a substance obtained from normal human plasma effective in accelerating the coagulation of hemophilic blood. *J. Clin. Investigation* 16:113-124, 1937.
- 5 Quick, A. J., Stanley Brown M., and Bancroft, F. W. A study of the coagulation defect in hemophilia and in jaundice. *Am. J. M. Sc.* 190:501-511, 1945.
- 6 Seggers, W. H., Brunkhaus, K. M., Smith, H. P., and Warner, E. D. The purification of thrombin. *J. Biol. Chem.* 126:91-95, 1938.
- 7 Whitehouse, H. B. The physiology and pathology of uterine hemorrhage. *Lancet* 1:877-885 and 951-957, 1914.
- 8 Whitehouse, B. Menstrual function with observations on the relation of Graafian follicle and corpus luteum to pathological uterine hemorrhage. *Lancet* 1:1275-1279, 1927.
- 9 Meigs, J. V. Personal communication.
- 10 Cove, J. R. *The Writings of Hippocrates and Galen*. 681 pp. Philadelphia: Lindsay and Blakiston, 1846. P. 293.

## BILE-DUCT RECONSTRUCTION WITH VITALLIUM TUBES\*

## Report of a Case

HOWARD M. CLUTE, M.D.†

BOSTON

STRICTURES of the common bile duct are almost invariably caused by an injury to the duct during some operation on the biliary tract. These surgical accidents carry in their train complications that are always serious and very frequently fatal, not only because of the accompany-

to-end sutures of the duct, transplantation of external biliary fistulas, anastomosis of the duct with the gastrointestinal tract, and replacement of the duct by a rubber tube have all been used.

Plastic repair of the duct in simple strictures and anastomosis of the common hepatic duct to

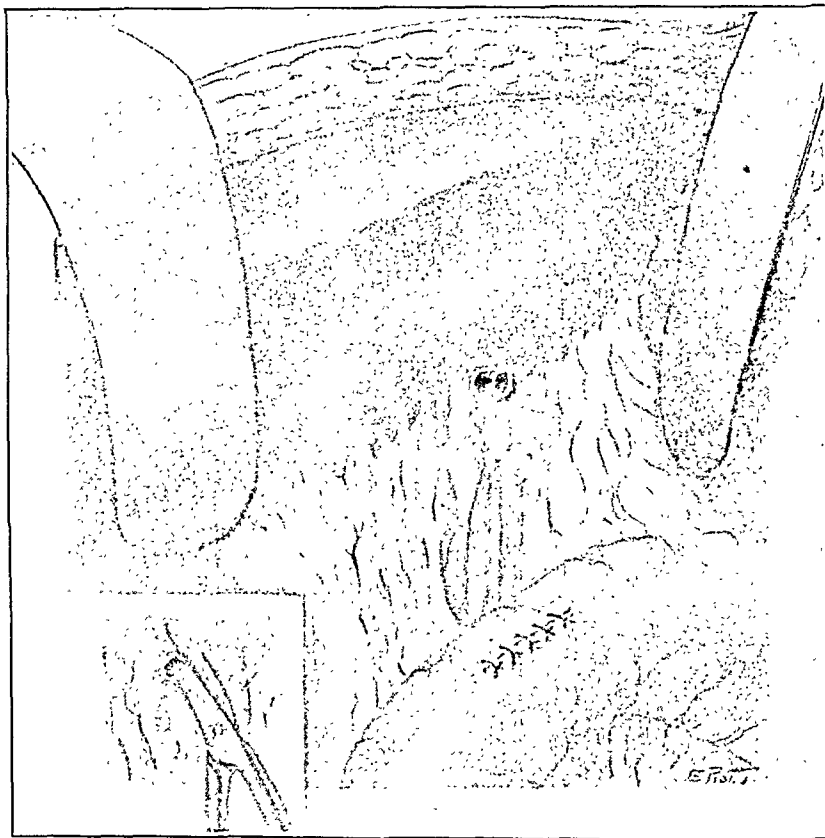


FIGURE 1.

*The strictured area high in the common hepatic duct has been exposed. The opening in the duodenal wall, remaining from the previous anastomosis of the duodenum to the common bile duct, was first used for retrograde catheterization of the common duct and then closed. The insert shows the cutting of the fibrous ring about the opening of the common hepatic duct.*

ing obstruction and infection of the biliary tract, but also because of the dangers and frequent failures that accompany attempts at surgical repair.

The methods used for the surgical repair of bile-duct strictures and injuries have been slowly developed over the last quarter of a century. Plastic repair of the bile duct on the Heineke-Mikulicz principle is the simplest device available. End-

the stomach or duodenum in the more serious strictures have given the best results. Transplantation of external biliary fistulas has had but little success, and is now rarely used. Replacement of a portion of the common bile duct by a rubber tube is successful so long as the lumen of the tube remains free of bile salts. Usually, however, the bile salts produce changes in the rubber tube, and deposits in its lumen sufficient to cause obstruction of the flow of bile. I removed one rubber tube from the common duct seven years after

\*Presented at the annual meeting of the New England Surgical Society, Hanover, New Hampshire, September 6, 1941.

†Professor of surgery, Boston University School of Medicine; surgeon-in-chief, Massachusetts Memorial Hospitals.

it had been inserted. There was almost complete obstruction of its lumen by bile salts and detritus, and the rubber itself was friable and crumbly. I have also seen deposits of bile salts in the lumens of T tubes that had been in place but a few weeks. It is generally admitted, I believe, that rubber tubing does not offer a safe medium for use in repairing serious injuries to the common bile duct.

It occurred to Dr. Herm in Pearce, of Rochester, New York, that a vitallium tube might be used

viously, and hemorrhage had occurred from the cystic artery. A clamp was hurriedly applied and left in place for 24 hours. It apparently included the cystic artery and the uppermost portion of the common hepatic duct in its grasp. The common duct was explored 4 months later, because of attacks of pain, fever, chills and jaundice. No stones were found. A stricture was discovered, but was considered inoperable.

At operation on July 27, 1939, I found a stricture, almost complete, very high in the common hepatic duct. The stricture was incised longitudinally, and a rubber T tube placed in it. The patient was well for 5 months with the tube in place. It was then accidentally pulled out. Soon after that, attacks of pain, chills, fever and jaundice recurred.

At operation on April 14, 1940, I exposed the strictured common duct with great difficulty. About 0.3 cm. of the common hepatic duct was present. The duodenum was freed, and a hepaticoduodenostomy was performed. A ring of fibrous tissue about the opening of the common hepatic duct made me fear that the new opening might contract and obstruct. After 6 or 7 months, this occurred, and the attacks of pain, chills, fever and jaundice returned.

On November 29, I again exposed the common duct area, cutting the duodenum free from its anastomosis to the



FIGURE 2

*The vitallium tube has been inserted into the stump of the common hepatic duct, being held in place with silk sutures. The distal portion of the common duct has been freed.*

to replace or reconstruct an injured common bile duct. He<sup>1</sup> showed that bile made no changes in vitallium, and he has successfully implanted vitallium tubes in 2 cases of common duct stricture. Through the kindness of Dr. Pearce, I was given an opportunity to employ this method in a very difficult common duct stricture. Vitallium tubes of the required type, which differ in shape from the ones used by Dr. Pearce, were obtained\*. The case is reported so that other surgeons may be familiar with the possibilities of vitallium tubes in bile duct strictures.

#### CASE REPORT

Mrs. M. L. (2488), a 38 year old woman, was admitted to the hospital on June 30, 1938. Cholecystectomy for gallstones had been performed elsewhere 16 months pre-

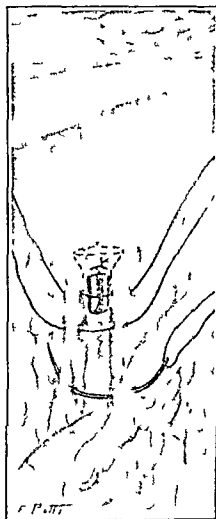


FIGURE 3

*The vitallium tube has been placed in the common duct. It should be noted that a portion of the duct is completely lacking. Continent fat tabs and omentum were used to cover the exposed tube.*

common hepatic duct. The anastomosis had diminished to pin point size. By means of an opening in the duodenum, a probe was inserted through the ampulla of Vater, and demonstrated the distal portion of the common duct. The duodenum was closed, and the common hepatic duct was dissected free as it lay in liver tissue (Fig. 1). Its opening was a ring of firm, fibrous scar tissue. In the hepatic ducts was much detritus, as well as many tiny

\* Manufactured by the Austral Laboratory, Incorporated, New York City.



black gallstones. The opening of this duct was enlarged so that the trumpet-shaped end of a vitallium tube could be inserted and held securely with silk sutures (Fig. 2). The distal end of the tube was placed in the distal portion of the common bile duct, about 2 cm. of which was absent. Omentum was brought in to surround the tube (Fig. 3). A jejunostomy was made for postoperative feeding. A

examination at this time showed no evident change in the position of the tube (Fig. 4). No further attacks have occurred, and the patient appeared to be very well when last seen (March, 1942).

The technical difficulties in this case were only those of exposing both the common hepatic duct

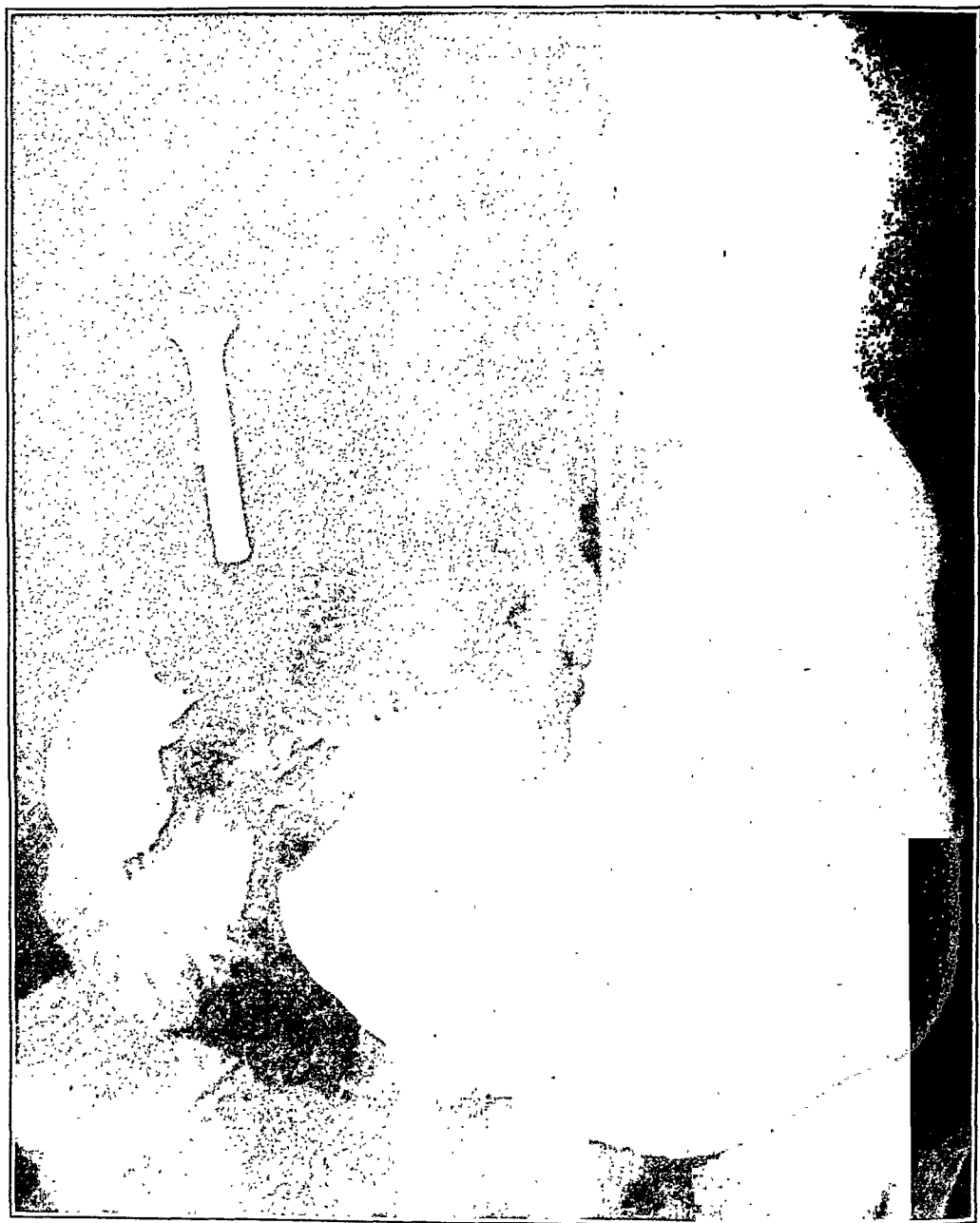


FIGURE 4.

*This x-ray film, taken some months postoperatively, shows the vitallium tube in the common bile duct and its relation to the barium-filled stomach.*

drain was placed in the region of the anastomosis, but not close to it.

Recovery was entirely uneventful, the highest temperature being 99.4°F. 2 days after operation. The patient was entirely well for 6 months and then had one attack of pain and transient jaundice. This was followed by a small wound infection that quickly cleared up. X-ray

above and the common bile duct below, in a field in which the landmarks had been largely concealed by inflammatory tissue and adhesions following the previous operations. Placing the tube in the bile duct was not difficult, because the diameter chanced to be just right; furthermore,

the ring of fibrous tissue in the common hepatic duct held the trumpetlike proximal end of the tube firmly in place. It is noteworthy that the

tion of a vitallium tube in the duct. I do believe, however, that such a tube can remain indefinitely in the body without being affected by the body

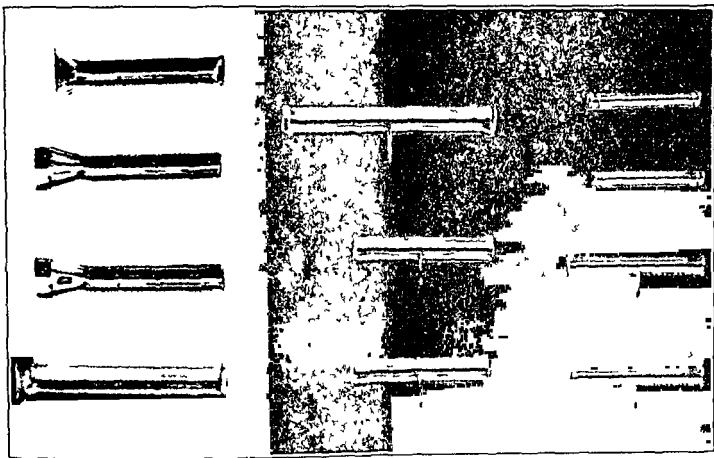


FIGURE 5 Types of Vitallium Tubes for Bile Duct Repair.

vitallium tube bridged a gap of about 2 cm in the bile duct.

Dr. Benjamin W. Seaman,<sup>2</sup> of Hempstead, New York, reports that his assistant, Dr. Carl Hettesheimer, has transplanted a vitallium tube into a strictured bile duct with success. An absence of about 2 cm of the common duct was replaced. The patient was well nearly four months after operation.

It is apparent that in the future one must have various sizes and shapes of vitallium tubes at hand for the different sized common ducts that may be encountered, although some alteration of the shape of the tubes can be made by cutting them with heavy scissors. In fact, it is now possible to obtain various shapes and sizes of tubes (Fig. 5).

I do not recommend that every case of stricture of the common bile duct be treated by implant-

fluids, and that increasing usefulness of such tubes will be evident. I am satisfied that, in the case reported, such a tube was of the greatest help to the surgeon, and a lifesaving device for the patient.

171 Bay State Road

#### REFERENCES

1. Pearse, H. E. Design structure of the bile ducts treated with a vitallium tube. *Surgery* 10:37-44, 1941.
2. Seaman, B. W. Personal communication.

#### Erratum

In the article, "The Treatment of Mammary Pain and Secretion with Testosterone Propionate," by Drs. Ira T. Nathanson, Joe V. Meigs and Langdon Parsons, which appeared in the February 26 issue of the *Journal*, the words "first" and "second" on page 324, column 2, lines 26 and 27, should be transposed.

## MEDICAL PROGRESS

### TRICHINOSIS AND ENTEROBIASIS: THEIR IMPORTANCE IN NEW ENGLAND\*

DONALD L. AUGUSTINE, Sc.D.†

BOSTON

FROM a review of the literature, it is evident that trichinosis still remains the most frequent and the most serious of the parasitic infections in New England. It is also clear that enterobiasis, or pinworm infection, is probably second in frequency. Although the latter is definitely less serious than trichinosis, its incidence is such as to be of notable concern among pediatricians and public-health workers.

#### TRICHINOSIS

The extraordinary frequency of trichinosis in the United States began to be appreciated when Queen,<sup>1</sup> in 1931, briefly reported that examinations of diaphragms from 344 consecutive cases at autopsy in Rochester, New York, showed 59 (17.5 per cent) infected with trichinae, and that in a similar study made on 58 cases at autopsy in Boston, 16 (28 per cent) proved to be trichinous. Queen's data were in sharp contrast to earlier estimations, which placed the incidence of infection from 0.5 to 2.0 per cent for most civilized countries. Some inadequate data, however, did indicate a much higher rate of infection for some parts of the United States. These early figures were based on direct microscopic examination of relatively small bits of muscle, whereas Queen utilized artificial digestion of 50-gm. portions of the diaphragm in his cases.

Shortly after the announcement of Queen's findings, similar surveys were undertaken in nearly every section of the country. The results of these local studies have shown an astonishingly high incidence of trichinosis throughout the whole United States, ranging from 3.5 per cent in New Orleans<sup>2</sup> to 36.0 per cent in Cleveland.<sup>3</sup> These recent data do not indicate, as they at first suggested, that trichinosis has been rapidly increasing in this country or in any section of this country. On the contrary, the situation is probably improved in many localities over that of fifty years ago. It should be recalled, however, that within recent years two major epidemics of trich-

inosis have occurred within the New England states, namely, the Portland epidemic of 1935, which involved 71 persons, with 2 deaths,<sup>4</sup> and the epidemic among members of the Civilian Conservation Corps at Camp Charles M. Smith, Waterbury, Vermont, three years later, in which there were 64 cases but no deaths.<sup>5</sup>

Human trichinosis almost invariably has its source in pork infected with encapsulated larvae of the parasite. As an exception, attention repeatedly has been called to California outbreaks of the disease, which originated from eating jerked bear meat. Recently, a number of cases have been reported from Germany, following the eating of game and fur-bearing animals; in several cases, the infection originated from nutrias.<sup>6</sup>

Trichinosis in swine is usually the direct result of their eating raw trichinous pork, either in garbage or in offal at the time of slaughter. The primary source of rat trichinosis is, like that for swine, raw; infected pork scraps in garbage collected for swine, or in scraps picked up in the market districts or at abattoirs. Because of the high frequency of trichinosis in rats, it has long been held that rats are important reservoirs of infection for the disease in swine. Although swine may eat dead rats thrown to them, they are seldom known to kill and eat rats, even when they are numerous in hog pens. For the most part, rats and pigs seem to get along on quite friendly terms.<sup>7-9</sup>

The infection in rats may be considerably spread through cannibalism, but such infection probably is rarely transmitted to swine. Thus, human, porcine and rat trichinosis are all chiefly of porcine origin.

Since the young trichinae, the progeny of the adult male and female worms in the intestine, are passively carried to all parts of the body by the lymph and blood streams, the question early arose concerning the possibility of prenatal infection, as in ascariasis, hookworm infection and several other parasitic worm infections in which a blood-stream invasion is characteristic in the developmental cycle. Hood and Olson,<sup>10</sup> in 1939, found trichinae in four diaphragms from 48 infants under one year of age, and suggested that prenatal trichinosis might be a common occurrence. The weight

Reprints of articles in this series are not available for distribution, but the articles will be published in book form. The current volume is *Medical Progress: Annual, 1940* (Springfield, Illinois: Charles C Thomas Company, 1941. \$4.00).

\*From the Department of Comparative Pathology and Tropical Medicine, Harvard Medical School and Harvard School of Public Health.

†Associate professor of comparative pathology and tropical medicine, Harvard Medical School and Harvard School of Public Health.

of careful experimental evidence, however, fails to confirm this conjecture.<sup>11-15</sup>

The cause for the failure of *Trichinella spiralis* to produce prenatal infection is not known. However, the migrating larva is strikingly less active as a tissue borer than the larvae of helminths that are known to produce prenatal infection. It is deposited directly into the lymph stream by the gravid female worm in the intestinal wall. Subsequently, it is passively carried by the blood through the lung capillaries into the arterial circulation. Its main active migration occurs when it passes from the blood vessels and penetrates a muscle fiber. If this larva fails to penetrate a striated, skeletal muscle fiber, it is quickly surrounded by a focus of acute inflammatory exudate and is destroyed. This is known to be the fate of larvae that emigrate from the vessels situated in the heart, pancreas and brain; and although no trichinae have been found in placental tissues, there is every reason to believe that some are carried to the placenta, where they are probably as effectively destroyed as in other sites not favorable for encapsulation. It appears, therefore, that the sluggish nature of the larva, together with the acute and effective response of the host against larvae that fail to become encapsulated within the striated muscle fibers, may account for the freedom of the fetus from this parasite.

Recent studies continue to stress the irregularity of the clinical course of trichinosis, and to emphasize clinical aids in the diagnosis of sporadic cases. Kaufman,<sup>16</sup> from a critical study of 12 misdiagnosed cases of trichinosis, reported one clue, which, if heeded, would have suggested the correct diagnosis, namely, a history of puffy eyelids in the patient or in a member of the immediate family, or an edema of the eyelids at the time of physical examination. He suggests that in taking a history in all acute illnesses, one make specific inquiry concerning the presence of puffy eyelids, and that if there is such a history, or if they are observed at examination, the diagnosis be seriously considered. Andes, Green and Breazeale<sup>17</sup> and Lee<sup>18</sup> similarly note that edema about the eyes is one of the commonest symptoms, even in mild infections. McNaught<sup>19</sup> has recorded a new symptom in cases of active trichinosis: so-called "splinter hemorrhages," which occur beneath and along the distal ends of the fingernail and toenail beds and form a crescentic band of ecchymosis. This manifestation appears not to have been recorded heretofore, but according to McNaught it may be expected in 60 to 70 per cent of the cases of clinical trichinosis. It furnished strong supportive evidence in diagnosis during the recent epidemics in Wolverhampton, England.<sup>19</sup> These subungual hemorrhages occur

at the time of invasion of the tissues by migrating larvae, and are of the nature of petechiae.

The presence of a blood eosinophilia, particularly a rapidly ascending eosinophilia, is generally held to be the most reliable sign of trichinosis.<sup>16-20</sup> The lack of an eosinophilia does not rule out the diagnosis, since this sign may be absent in severe fatal cases or in trichinosis complicated by a concurrent bacterial infection.<sup>20, 21</sup>

Laboratory procedures for demonstrating the presence of the parasite during the life of the patient have not been improved materially. Although migrating trichinae have been found in the blood and spinal fluid, young and encapsulated larvae in excised bits of skeletal muscle and adult worms and larvae in evacuated stools after drastic purgation, direct evidence of the parasite is usually not readily obtained.

Dammin<sup>22</sup> reports the ready finding of larvae in arterial blood from a case of trichinosis after unsuccessful examination of venous and capillary blood. He suggests the examination of arterial blood instead of venous blood.

For post-mortem examination, the compressor method and the combined digestion-Baermann method described by Nolan and Bozicevich<sup>23</sup> have been widely and successfully used. The first procedure consists in the compression of a 1-gm. sample of muscle, cut into small pieces between plate-glass slides, and examination with a low power of a dissecting microscope. The digestion-Baermann method utilizes the digestion of ground, striated muscle in artificial gastric juice; the diluted digestate is placed in a Baermann apparatus (used in hookworm studies for isolating infective hookworm larvae from soil samples), which is essentially a large funnel with a sieve that screens out the coarser particles and permits the trichinae to settle in the neck of the funnel. The compressor method has been particularly useful in detecting long-standing infections in which the trichinae are dead and calcified and would be missed with the digestion-Baermann method. The digestion-Baermann method has been used in the majority of the recent incidence studies.

Serologic and skin tests have been widely used for more than ten years. The results of observers who have had the most experience with these tests indicate that they are specific and of definite value as diagnostic aids.<sup>5, 20, 21-28</sup> In the experience of McNaught, Beard and Meyers,<sup>28</sup> the skin and precipitin tests have shown as high a degree of sensitivity as is found in any other clinical or laboratory procedure. However, limitations of these reactions for accurate diagnosis should be kept in mind. In view of the high percentage of people harboring the parasite, it is to be expected that some patients will give positive

reactions even though their illness may not be related to acute trichinosis. It was shown<sup>29</sup> and has recently been confirmed<sup>30</sup> that tissue and serum sensitivity to trichinella antigen may be present for years after a person has recovered from an attack of trichinosis. Thus, negative tests are more reliable in ruling out trichinosis than positive tests are in establishing the diagnosis.

Two types of skin reactions may develop in trichinous cases: delayed and immediate. The delayed reaction occurs during the first week of illness, and is similar to the delayed tuberculin reaction. After a second week, the skin reaction is immediate, consists of a blanched wheal surrounded by a zone of erythema, and gradually disappears about one hour after the antigen has been injected. The precipitin test does not become positive until about the fourth week of illness. It is especially useful if at first negative and later positive. For years, a chief objection to these tests was the difficulty in preparing or obtaining the antigen. At present, however, it can be obtained from at least two of the leading firms in this country that supply other biologic preparations.

A question of particular interest and one that is frequently raised in civil-court cases, is whether the patient suffers permanent injuries following recovery from acute trichinosis. Theiler, Augustine and Spink<sup>29</sup> elicited no residual symptoms from 7 patients seen from four to seven years after recovery. Warren, Drake and Hawkes<sup>30</sup> make no mention of any residual symptom in 45 patients examined three years after recovery from acute trichinosis.

The electrocardiographic findings of Spink<sup>31</sup> on 18 patients with trichinosis showed that myocardial damage, in recovered cases, is temporary. One of these patients, who showed marked signs of a weakened myocardium on the seventeenth day of illness, had a normal electrocardiogram thirty-two days later, the forty-ninth day after onset. Seven months later, the patient, on examination, complained of weakness, pain in the muscles of the extremities, dyspnea and palpitation on exertion, and slight edema of the ankles. The heart rate was regular, no murmurs were heard, and the blood pressure was 106 systolic, 70 diastolic. An electrocardiogram was normal. Beecher and Amidon<sup>32</sup> similarly reported only temporary cardiac damage in 44 cases of trichinosis followed by clinical and electrocardiographic examination.

Experimental evidence clearly supports these clinical deductions on myocardial injury in trichinosis. Graham,<sup>33</sup> in 1897, showed that myocarditis in trichinous rats is the direct result of the presence of young trichinae in the myocardium, although the muscle fiber is not penetrated. In

Graham's experiments, the greatest number of larvae occurred in the heart muscle on the ninth day of infection, and very few larvae, if any, were definitely recognized after the fourteenth day. It therefore appeared that the developing trichinae either had been killed in situ or had left the myocardium by passing back into the circulation. Zoller<sup>34</sup> confirmed Graham's findings and expressed the belief that the injury to the heart muscle was only temporary. Dunlap and Weller,<sup>35</sup> studying the disease in white rats, found myocardial damage during the period of active dissemination of the trichinae, beginning as early as five days after infection, but it was not observed as soon as active migration of the larvae had ceased. No notable alteration of myocardiac tissue was found.

Most and Abeles<sup>36</sup> have contributed a comprehensive review of the literature relating to clinical manifestations and neuropathologic changes in trichinosis of the nervous system; they report 2 of their cases, 1 of which was fatal. The patient who on admission presented signs of mild, acute encephalitis made an uneventful recovery. Thirty-one days after admission, the neurologic and mental status of this patient was normal. From the review of the literature by Most and Abeles, it appears that no extensive damage to the nervous system is to be expected in trichinosis. Berco-vitz<sup>37</sup> searched for residual symptoms of trichinosis in 70 patients recovered from one month to two years prior to his examination. He reported that of these patients, some of whom had suffered severely from the disease, 52, or 74 per cent, suffered no residual symptoms between one month and one year after recovery. Muscle weakness and muscle soreness were the chief complaints of the patients with symptoms, and these lasted for varying periods, but not longer than one year. In no case was there anything resembling a permanent disability.

From the information available, it appears evident that, at the most, vague muscle pains and ready fatigue may be expected to persist for some months after apparent recovery from trichinosis, but the repair of damage to the heart or other tissues in which the parasite does not successfully develop during the acute stage of illness is complete, and probably never results in a permanent disability.

In addition to the vast amount of study on the serologic reactions in trichinosis, there has been, during recent years, an ever-increasing interest in its immunity relations.

Without question, no other parasitic worm has so broad a host range as *T. spiralis*. Although the principal hosts, or the hosts most frequently

parasitized under natural conditions, are rats, swine and man, in all probability, any mammal can serve as a favorable host. In addition to these hosts, natural infections are now recorded in mice, domestic cats, palm civets, dogs, wolves, coyotes, foxes, pole cats, martins, ferrets, nutrias, European and American badgers, raccoons, polar bears, common bears and mongooses. Experimentally infected animals include guinea pigs, rabbits, hamsters, monkeys, sheep, cattle, gophers, horses, chickens, pigeons, magpies and rooks. Only young chickens are susceptible to muscular infection, which is of short duration.<sup>38</sup> Normal adult birds appear highly refractory to trichinosis, but muscle infection has been established in adult pigeons affected by avitaminosis.<sup>39</sup> Cold-blooded animals, fish and frogs appear to possess an absolute natural immunity against the parasite.<sup>40, 41</sup>

Recent investigations show that the diet of the host may significantly influence natural resistance to trichinosis. For example, McCoy<sup>42</sup> observed that young rats kept on a diet deficient in vitamin A are markedly more susceptible to the disease than those maintained on an adequate diet. The lowered resistance in the deficient rats was manifested by a persistence of the adult worms in the intestine, and also by the failure of these rats to develop any immunity against reinfection. Again, a diet lacking in vitamin E appears to enhance slightly the resistance of rats.<sup>43</sup>

It has been shown that animals that have recovered from an initial infection with *T. spiralis* resist reinfection.<sup>44-46</sup> When heavy doses of trichinae are fed to rats recovered from three or more sublethal infections, most of the trichinae are expelled after a few hours from the intestine.<sup>47</sup> Severe diarrhea is characteristic in reinfection in animals. It appears that the intestinal tract of the immune animal is "sensitized" following previous infection, and that the worms are thereby rapidly expelled on reinfection.<sup>20</sup> Whether recovery from an initial infection confers similar immunity in man is not known. It seems possible, however, that when the disease in man is marked by acute gastrointestinal symptoms and is not followed by other symptoms, the patient may have recovered from a previous infection.

Mauss<sup>15</sup> reported that the offspring of trichinosis rats, rabbits and hamsters are less susceptible to trichinosis than the offspring of uninfected mothers. This lowered susceptibility is of short duration, being lost within about three weeks of birth. The transmission presumably occurs through the mother's milk.

Artificial immunity to *T. spiralis* has been produced by intraperitoneal injection of living larvae, of heat-killed larvae or of dried and powdered

larvae.<sup>48</sup> The resistance induced by these methods is not so great as that brought about by active infection.

Conflicting results have been obtained from experiments on passive transfer of acquired immunity to trichinosis. Claims of beneficial results in acute cases of the disease in human beings by the use of serum from patients recovered from the infection<sup>49</sup> are not generally supported by animal experimentation. Culbertson and Kaplan<sup>50</sup> recorded passive immunization of mice by the injection of immune rabbit serum. The degree of resistance induced was very low. McCoy<sup>48</sup> obtained no evidence that immunity to trichinosis can be transferred passively by the use of serum from superinfected animals.

New light on the mechanism of immunity to trichinosis has been presented by Oliver-González.<sup>51</sup> According to him, two types of antibody appear in the serum of rats as a result of infection with *T. spiralis*—one acts specifically on the adult worms, and the other on the larvae. The former appears in the serum about the fifteenth day after infection, disappears by the fiftieth day and reaches its highest titer during repeated superinfection. By passive transfer, it partially protects rats against the intestinal stage of infection. In vitro, it causes precipitation at the mouth, anus and vulva of the female worms, and this is sometimes followed by death of the adult worms. The antilarval substance, which does not appear in the serum until about the thirtieth day after infection, reaches its highest titer about the fiftieth day after infection, but is not increased during repeated superinfections. In vitro, it causes oral, but no anal, precipitation, and sometimes death of the larvae. It gives little or no protection to rats against the intestinal stage of trichinosis.

From the results of Oliver-González's<sup>51</sup> studies, it is apparent that the varying results of earlier workers on passive transfer of acquired immunity to trichinosis may be attributed to the use of serums taken too long after infection, that is, at a time when the antibody content of the serum is low or absent and, particularly, in experimental studies, to the use of rats and guinea pigs, which, according to Oliver-González, do not produce such potent antibodies as rabbits do.

Experimental studies have failed to reveal a specific drug either for the removal of adult worms from the intestine or for the destruction of larvae in the blood stream and muscles. Results from the use of calcium lactate, parathormone, irradiated ergosterol and related substances forcing calcification of encapsulated trichinae in experimental animals do not warrant their use in the treatment of human infection.<sup>52</sup>

Although much has been written and said, little has been accomplished within recent years in the prevention and control of trichinosis. Until drastic changes are made in the methods of garbage disposal throughout the country, the only effective means of control must remain with the housekeeper, which means that all pork must be cooked thoroughly before it is eaten.

#### ENTEROBIASIS

*Enterobius vermicularis*, the pinworm, is a parasite of human beings only. It occurs, in its various stages of development, from the lower ileum through the rectum. Unlike those of other intestinal worms, the eggs of the pinworm are not deposited in the intestinal tract. The gravid female worm characteristically migrates down the large intestine and through the rectum, especially at night, and lays her eggs on the perianal skin of the patient. The worms may travel a distance of several centimeters from the anus within an hour after the patient has retired.<sup>53</sup> Locomotion, however, ceases soon after exposure to the air. The eggs are then discharged by violent uterine contractions, and masses of eggs appear at the region of the vulva of the worm. The spent female worm then becomes shriveled and may drop from the body into the bed clothing.

Owing to this peculiar behavior of the female worm during oviposition, the usual methods of examination of feces for parasites are wholly inadequate and unreliable for detecting pinworm eggs. Thus far, the most reliable means of diagnosis has been the finding of the eggs collected in scrapings from the perianal skin. Several techniques have been recommended for obtaining the eggs, such as the use of spoons, glass tubes and rods, spatulas and cotton pledgets, of which the first practical and efficient procedure was devised by Hall in 1937.<sup>54</sup> By Hall's method, the tip of a glass rod is covered with a square of cellophane held in place on the rod by a rubber band. The opposite end is carried through a rubber cork fitted into a glass tube, which prevents drying and loss of material during transportation and ensures safety of the carrier from infection. The swab has been generally referred to in the literature as the N. I. H. (National Institute of Health) swab.

To obtain a specimen for examination, the cellophaned end of the swab is passed radially among the perianal folds and over the neighboring perineum. Subsequently, the piece of cellophane, with the scrapings adhering to it, is removed from the glass rod and placed, face down, over two drops of physiologic saline solution, and examined under the microscope. In addition to the eggs

of the parasite, vestiges of female worms or whole female worms may be present in the scrapings. Swabs should be taken during the night or in the morning before the patient bathes or defecates, preferably on at least seven days if the first results are negative.

Since the introduction of the N. I. H. swab, new studies on the incidence and epidemiology of enterobiasis have appeared in rapid succession. Cram<sup>55</sup> has summarized the results of various investigators on the incidence of pinworm infection, as revealed by the use of the N. I. H. swab, in the United States, Puerto Rico, Canada and the Philippines. Of a total of 22,376 persons examined, 9703, or 43 per cent, were positive. The distribution of positive cases is not spotted, as might be expected. The infection appears to be astoundingly high in the Boston area. Weller and Sorenson,<sup>56</sup> in 1941, in a clinical study of 505 white children, between the ages of two and twelve years, living in the Boston area, found 97, or 19.2 per cent, infected. In this group, 415 children were examined with one swab only. Of these, 74 cases, or 17.7 per cent, were positive. The remaining 90 cases were examined with two swabs. Of these, 23 cases, or 25.5 per cent, were positive. These later data illustrate the value of repeated swabs in diagnosis. It is probable that the findings of Weller and Sorenson may reflect quite well the frequency of pinworm infections in children throughout New England.

Recent studies have emphasized the familial nature of pinworm infection. Multiple cases are the rule rather than the exception, and frequently all the children of the family are infected, as well as one or both of the parents. Although families with pinworm infections are found most frequently in older, congested, residential sections, pinworm infections are not confined to any section or to any socioeconomic level.

Clinical symptoms in pinworm infection are exceedingly variable in both their nature and degree, being apparently absent in some cases and severe in others. The greater proportion of the cases studied by Weller and Sorenson<sup>56</sup> were essentially asymptomatic, although anal pruritus, skin lesions, enuresis, loss of appetite and masturbation were commoner in the children with pinworms than in those who did not have pinworms. Brady and Wright<sup>57</sup> noted gains in weight, improvement in color, disappearance of dark circles under the eyes, improved appetite and, particularly, improved social attitude and scholastic standing in many infected children after successful treatment. These authors did not find that enuresis, frequently attributed to pinworm infection, occurred with any greater frequency in their

infected than in their noninfected group. It appears, however, that pinworm vaginitis occurs much more frequently than has been generally considered in the past. Of 45 cases in young girls examined by Brady and Wright, 14, or 31 per cent, were positive on one vulvar swab made at the introitus. Ten girls showed a mucoid vaginal discharge believed to be due to irritation of the genital tract from parasites migrating between the labia and into the vagina.

Africa<sup>58</sup> has summarized the literature on reported cases of enterobiasis in which pinworms migrated through the vagina and uterus into the fallopian tubes, causing symptoms of salpingitis, or into the peritoneal cavity, where they were found encapsulated in the peritoneum. He points to the fact that all such cases were observed accidentally during operation or at autopsy, which indicates that the condition may not be unusual, and that, obviously, many cases must have escaped notice.

The role of the pinworm in appendicitis is still an unsolved problem. Botsford, Hudson and Chamberlain<sup>59</sup> have expressed the opinion that the parasite may give rise to the syndrome of appendicitis without characteristic histologic changes. According to Chandler et al.,<sup>60</sup> it is only the fourth-stage larva of *E. vermicularis* that habitually burrows into mucous membranes, especially of the appendix, and there is a definite period six to nine days after infection when symptoms of invasion appear, followed four to seven days later by migrating worms from the anus. It appears, therefore, that the transient nature of the pinworm in the wall of the appendix may explain the many failures in demonstrating the worm at operation; because of these failures, the conception has become current that the parasite is not an important factor in appendicitis.

Wright, Brady and Bozicevich,<sup>61</sup> in 1938, recommended gentian violet for the treatment of enterobiasis; they obtained a cure rate of over 90 per cent, as indicated by the N. I. H. swab technic. The results of further tests on the specificity of the gentian violet for pinworms by D'Antoni and Sawitz,<sup>62</sup> Miller and his associates<sup>63</sup> and Wright and Brady<sup>64</sup> uphold the early results of Wright, Brady and Bozicevich. For adults, the recommended dose is 0.065 gm. (1 gr.) of the drug in a water-soluble, coated, four-hour type tablet given three times daily before meals for a period of eight days, followed by a seven-day rest period, after which treatment is repeated for eight additional days. For children, the recommended daily dosage is 0.01 gm. (1/4 gr.) for each year of apparent age. According to the authors cited above, the

drug, in general, is well tolerated. Contraindications include concomitant Ascaris infection, any disease of the gastrointestinal tract, cardiac, hepatic or renal disease and pregnancy.

The control of pinworm infection is exceedingly difficult. The pinworm differs in its development from all other nematodes infecting man. The egg requires no prolonged period of incubation before it reaches the infective stage. When laid, the egg already contains an embryo, which becomes fully developed and infective on the skin of the patient within six hours. Infection is direct, that is, it follows ingestion of this egg.

During the last few years, particular attention has been given by investigators to the mechanism of pinworm infection. The infected patient may readily contaminate the hands while scratching the perianal regions to relieve itching caused by migrating worms, or when using the toilet. Pinworm eggs have been removed so frequently from under the fingernail that the examination of such scrapings has been advocated as a means of establishing the diagnosis. Sooner or later, the eggs on the hand are carried to the mouth of infected persons (autoinfection), or they may contaminate objects that can carry the infection to other persons. There is definite evidence that pinworm eggs may be carried about by air currents. Lentze<sup>65</sup> demonstrated experimentally that viable pinworm eggs could remain suspended in air for two minutes, and, on conclusion of the experiment, recovered eggs from his own nasal passages. Particularly important, at this time, are the epidemiologic studies on pinworm infection by Nolan and Reardon,<sup>66</sup> D'Antoni and Sawitz<sup>62</sup> and Sawitz, D'Antoni, Rhude and Lob.<sup>67</sup> Nolan and Reardon studied the distribution of pinworm eggs in household dust from seven homes, in each of which at least one member of the family was heavily infected. Viable eggs were found in dust taken from the floor and furniture and from the top molding of doorways and ceiling lights. Although the contamination of the furniture might have come directly from infected persons, the finding of viable eggs at the higher levels definitely points to air transportation. D'Antoni et al. obtained similar results from their study at six institutional homes for children. Viable eggs were found in all samples of dust collected in the dormitories from floor cracks, ledges of pillars of doors, windows and toilet partitions, at heights under eight feet from the floor. From these studies, it appears that the obstinate infection, which may persist for months or even years in spite of repeated anthelmintic treatment, is more probably the result of constant reinfection, frequently air borne,



than of an internal multiplication and development of the worms, as generally held in the past, but lacking confirmation.

Pinworm eggs are markedly resistant to physical and chemical agents. A temperature of 55°C. and above kills the eggs in a few seconds. At body temperature and on a damp base,—as on the human skin, especially under the fingernails,—they may survive for about ten days.<sup>65</sup>

Jones and Jacobs,<sup>68</sup> in a critical study on the survival of pinworm eggs under known conditions of temperature and humidity, found temperatures above 28°C., with humidities below 50 per cent, definitely destructive within twenty-four hours. None of the eggs survived after sixteen hours at a temperature of 36°C. and a relative humidity of 38 to 41 per cent. In water, at 3 to 5°C., the eggs survived for eighteen days. Ordinary disinfectants in strengths commonly used in the home do not kill pinworm eggs.

The futility of attempting to control pinworm infections in a household by hygienic measures alone was demonstrated in 1940 by D'Antoni et al.<sup>62, 67</sup> A vigorous cleanliness program was put into force for six weeks in a children's home that had been kept scrupulously clean. At the beginning of the experiment, extra housemaids cleaned every room with hot water and soap daily, and at night the children wore short cotton pants, which were changed and sterilized daily. Bed sheets were changed and sterilized daily, and underwear was changed daily and sent to the laundry. Nail brushes were provided for each child, and their use was enforced. Two showers were taken daily, instead of one. At the close of the experiment, swab examinations showed an increase from 38 to 51 per cent in the incidence of pinworms. In a similar home, treatment included prolonged use of gentian violet without special hygienic measures. Post-treatment swabs showed that a cure of approximately 90 per cent had been obtained.

Thus, hygienic measures alone appear to be of little value in the eradication of pinworm infection in the household, and control lies in simultaneous medical treatment administered to all infected persons within the household for a time sufficiently long to cover the period of survival of eggs in the surroundings.

## REFERENCES

- Queen, F. B. The prevalence of human infection with *Trichinella spiralis*. *J. Parasitol.* 18:123, 1931.
- Hinman, E. H. Trichiniasis in Louisiana. *New Orleans M. & S. J.* 88:445-448, 1936.
- Evans, C. H., Jr. Trichinosis in Cleveland: postmortem examination of diaphragm and skeletal muscles from 100 consecutive autopsies. *J. Infect. Dis.* 63:337-339, 1938.
- Drake, E. H., Hawkes, R. S., and Warren, M. An epidemic of trichinosis in Maine. *J. A. M. A.* 105:1340-1343, 1935.
- Ferenbaugh, T. L., Segal, L., and Schulze, H. A. A trichinosis epidemic of sixty-four cases. *J. A. M. A.* 110:1434-1436, 1938.
- Rubli, H. Trichinose beim sumpfbiber, *Myocastor coypus*. *Schweiz. Arch. Tierheilk.* 78:420-424, 1936.
- Mark, E. L. Trichinae in swine. *Twentieth Annual Report of the Massachusetts State Board of Health*. Public Document No. 34. Pp. 113-134, 1889.
- Spink, W. W., and Augustine, D. L. Trichinosis in Boston. *New Eng. J. Med.* 213:527-531, 1935.
- Hall, M. C. Studies on trichinosis. VII. The past and present status of trichinosis in the United States, and the indicated control measures. *Pub. Health Rep.* 53:1472-1486, 1938.
- Hood, M., and Olson, S. W. Trichinosis in the Chicago area. *Am. J. Hyg.*, Sect. D 29:51-56, 1939.
- Stäubli, C. Trichinosis. Wiesbaden: J. F. Bergmann, 1909.
- Augustine, D. L. Studies on the subject of prenatal trichinosis. *Am. J. Hyg.* 19:115-122, 1934.
- Roth, H. Ein Beitrag zur Frage der prenatalen Trichineninfektion. *Acta Path. et microbiol. Scandinav.* 12:203-215, 1935.
- Catron, L. Non-transmissibility in utero of trichinosis in the rat. *Proc. Soc. Exper. Biol. & Med.* 36:721-723, 1937.
- Mauss, E. A. Transmission of immunity to *Trichinella spiralis* from infected animals to their offspring. *Am. J. Hyg.*, Sect. D 32:55-73, 1940.
- Kaufman, R. E. Trichiniasis: clinical considerations. *Ann. Int. Med.* 13:1431-1460, 1940.
- Andes, J. E., Greene, R. A., and Breazeale, E. L. Early mild infestation with parasite *Trichinella*: report of ten cases. *J. A. M. A.* 114:2271-2275, 1940.
- Lee, J. E. S. An outbreak of trichinosis in Wolverhampton and district: a clinical report of seven cases. *Brit. M. J.* 1:237-240, 1941.
- McNaught, J. B. The diagnosis of trichinosis. *Am. J. Trop. Med.* 19:181-192, 1939.
- Spink, W. W., and Augustine, D. L. The diagnosis of trichinosis with especial reference to skin and precipitin tests. *J. A. M. A.* 104:1801-1805, 1935.
- Spink, W. W. The effects of vaccines, bacterial and parasitic infections on eosinophilia in trichinosis animals. *Arch. Int. Med.* 54:555-567, 1934.
- Dammin, G. J. Trichinosis: report of a case, with demonstration of the larva in the arterial blood. *New Eng. J. Med.* 224:357-360, 1941.
- Nolan, M. O., and Bozicevich, J. Studies on trichinosis. V. The incidence of trichinosis as indicated by postmortem examinations of 1,000 diaphragms. *Pub. Health Rep.* 53:652-673, 1938.
- Otto, G. F., and Jannet, J. H., Jr. A study of trichinosis in a Maryland family. *Am. J. Hyg.* 25:76-85, 1937.
- Sawitz, W. Prevalence of trichinosis in the United States. *Pub. Health Rep.* 53:365-383, 1938.
- Schapiro, M. M., Crosby, B. L., and Sickler, M. M. The correlation of clinical diagnosis and post-mortem findings in trichinosis. *J. Lab. & Clin. Med.* 23:681-687, 1938.
- Murphy, F. D., James, H. D., and Rasteller, J. W. Trichinosis: study of twenty-three cases. *Am. J. M. Sc.* 199:328-338, 1940.
- McNaught, J. B., Beard, R. R., and Meyers, J. D. The diagnosis of trichinosis by skin and precipitin tests. *Am. J. Clin. Path.* 11:195-209, 1941.
- Theiler, H., Augustine, D. L., and Spink, W. W. On the persistence of eosinophilia, and on immune reactions in human trichinosis, several years after recovery. *Parasitology* 27:345-354, 1935.
- Warren, M., Drake, E. H., and Hawkes, R. S. Some observations on the persistence of the Bachmann skin test and of eosinophilia after recovery from trichinosis. *Ann. Int. Med.* 13:2140-2146, 1940.
- Spink, W. W. Cardiovascular complications of trichinosis. *Arch. Int. Med.* 56:238-249, 1935.
- Beecher, C. H., and Amidon, E. L. Electrocardiographic findings in forty-four cases of trichinosis. *Am. Heart. J.* 16:219-224, 1938.
- Graham, J. Y. Beiträge zur Naturgeschichte der *Trichina spiralis*. *Arch. f. mikr. Anat.* 50:219-275, 1897.
- Zoller, H. Über die Herzmuskelerkrankung im Verlauf der Trichinose. *Virechows Arch. f. path. Anat.* 265:430-443, 1927.
- Dunlap, G. L., and Weller, C. V. Pathogenesis in trichinosis myocarditis. *Proc. Soc. Exper. Biol. & Med.* 30:1261, 1933.
- Most, H., and Abeles, M. M. Trichiniasis involving the nervous system: a clinical and neuropathologic view, with report of two cases. *Arch. Neurol. & Psychiat.* 37:589-616, 1937.
- Bercovitz, Z. Residual symptoms in patients following recovery from acute infestation with trichinosis. *Am. J. Trop. Med.* 20:849-857, 1940.
- Augustine, D. L. Experimental trichinosis in chicks. *Science N. S.* 78:608, 1933.
- Pavlov, P. Ricerche sperimentali sulla trichinellosi dei volatili. *Riv. di parasitologia* 4:175-187, 1940.
- Idem. Recherches expérimentales sur la trichinose des volatiles et des vertébrés à sang froid. *Ann. de parasitol.* 15:440-447, 1937.
- Ransom, B. H. Trichinosis. *Report of the 18th Annual Meeting, United States Live Stock Sanitary Association*, 1915.

42. McCoy O R Effect of vitamin A deficiency on resistance of rats to infection with *Trichinella spiralis* *Am J Hyg* 20 169 180 1934
43. Zaman H The effect of host vitamin E deficiency on *Trichinella spiralis* infections *J Parasitol*, Supp 26 44, 1940
44. Ducat R *L'immunité dans la trichinose* Paris Thesis No 227 Pp 147 1921
45. McCoy O R Immunity of rats to reinfection with *Trichinella spiralis* *Am J Hyg* 14 454 494 1931
46. Kell H Experimental studies on the course of trichina infection in guinea pigs II Natural susceptibility of the guinea pig to experimental trichina infection *Am J Hyg* Sect D 29 83 104 1939
47. McCoy O R Rapid loss of *Trichinella* larvae fed to immune rats and its bearing on the mechanism of immunity *Am J Hyg* Sect D 32 105 116 1940
48. Idem Artificial immunization of rats against *Trichinella spiralis* *Am J Hyg* 21 200 213 1935
49. Sulzer B F A study of an epidemic of fourteen cases of trichinosis with cures by serum therapy *J A M A* 67 579 1916
50. Culbertson J T, and Kaplan S S A study upon passive immunity in trichinosis *J Parasitol* 30 156 166 1938
51. Oliver González J The dual antibody basis of acquired immunity in trichinosis *J Infect Dis* 69 254 270 1941
52. von Brand F, Otto G F, and Abrams F Forceful calcification with parathormone in experimental trichina (*Trichinella spiralis*) infection *Am J Hyg* Sect D 27 461 470 1938
53. Bozicevic J and Brady F J Studies on oxyuriasis XV A study of five hundred and four boys in a boys camp *M Ann District of Columbia* 7 187 190 1938
54. Hall M C Diagnosis of oxyuriasis types of anal swabs and scrapers with a description of an improved type of swab *Am J Trop Med* 17 445-453 1937
55. Cram E B *Enterobius vermicularis* Christie's *An Introduction to Nematology* Babylon New York 1941 Pp 322 324
56. Weller T H, and Sorenson C W Enterobiasis its incidence and symptomatology in a group of 505 children *New Eng J Med* 224:143 146 1941
57. Brady F J and Wright W W Studies on oxyuriasis XVIII The symptomatology of oxyuriasis as based on physical examinations and case histories on 200 patients *Am J M Sc* 198 367 372 1939
58. Africa C M On some possible hazards of *Enterobius* infection *Mod Med Tokyo* August 1938 Pp 13 19
59. Botsford T W Hudson H W and Chamberlain J W Pinworms and appendicitis *New Eng J Med* 221 933 936 1939
60. Chandler A C Alicata J E Chittwood T H, and Chittwood M B Life history (Zooparasitica) Parasites of vertebrates Christie's *An Introduction to Nematology* Babylon New York, 1941 Pp 267 301
61. Wright W H Brady F J and Bozicevic J Studies on oxyuriasis VIII A preliminary note on therapy with gentian violet *Proc Helminth Soc Washington* 5 5 7 1938
62. D'Antoni J S and Sawitz W The treatment of oxyuriasis *Am J Trop Med* 20 377 383 1940
63. Miller M J Choquette L Audet W Kelso R F and Guenette J A Studies on pinworm infection II Tests with gentian violet in the treatment of pinworm infection *Canad M A J* 43 455-458, 1940
64. Wright W H, and Brady F J Studies on oxyuriasis VIII The efficacy of gentian violet in the treatment of pinworm infestation *J A M A* 114 861 866 1940
65. Lentze P A Zur Biologie des *Oxyuris vermicularis* *Zentralbl f Bakt* (Abt I) 135 156 159 1935
66. Nolan M O and Reardon L Studies on oxyuriasis XX The distribution of the ova of *Enterobius vermicularis* in household dust *J Parasitol* 25 173 177, 1939
67. Sawitz W, D'Antoni J S Rhude K, and Lob S Studies on the epidemiology of oxyuriasis *South M J* 33 913 922 1940
68. Jones M F and Jacobs L Studies on oxyuriasis XXIII The survival of eggs of *Enterobius vermicularis* under known conditions of temperature and humidity *Am J Hyg* Sect D 33 88 107 1941

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTE-MORTEM AND POST-MORTEM RECORDS AS USED  
IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

### CASE 28121

#### PRESENTATION OF CASE

*First admission.* A forty-four-year-old chauffeur was admitted to the hospital because of epigastric discomfort, chills and jaundice of about three days' duration, following a long story of related complaints.

Twenty-six years before entry, the patient was confined to bed for six months by an illness characterized by abdominal pain, jaundice, edema and passage of bloody stools. He had a temperature of 105°F. for one month, and subsequently lost his hair and desquamated extensively. Following recovery, he was well for a long time. Ten years before entry, he experienced an attack of "gas in the stomach," accompanied by jaundice, lasting two days. Seven years before entry, following breakfast, he developed a sharp midepigastriac pain, which responded well to morphine given by a physician. Jaundice and fever followed, and the patient was therefore taken to a hospital, where roentgenograms were said to show an inflamed, stoneless gall bladder. While in that hospital, he suddenly "vomited bile," and was immediately relieved of his pain. After this episode, he had occasional spells of upper abdominal discomfort, sometimes followed by a yellowing of the scleras. He avoided fatty foods, on the advice of a physician. Four days before entry, he returned home from a trip in the country, feeling very tired. He noted slight epigastric discomfort, but this went away the next morning. This abnormal sensation, described as a "gripping, uncomfortable feeling, not exactly a pain," reappeared in the afternoon. It did not radiate or extend from the midepigastrium. Again, it was relieved when the patient lay down to rest. That night, a mild chill occurred, followed by sweating. On the morning of the second day before entry, the gripping sensation returned. The patient felt ill, and fasted. His physician found that he had a temperature of 101°F., that the scleras were jaundiced, and that the urine was "very dark orange." On the day preceding entry, the skin felt itchy, the jaundice was deeper, and the stools were clay colored.

On admission, the patient was mildly jaundiced. His general condition seemed good. There was slight tenderness in the epigastrium (positive

Murphy's sign). The liver edge was just palpable. Examination of the heart and lungs was negative.

The temperature, pulse and respirations were normal. The blood pressure was 138 systolic, 98 diastolic.

Examination of the blood showed a white-cell count of 8700 with 75 per cent polymorphonuclears, and a red-cell count of 4,440,000 with 95 per cent hemoglobin. The hematocrit was 53.4 per cent. The blood sugar was 77 mg. per 100 cc., the chloride was 97.2 millicequiv. per liter, and the nonprotein nitrogen was 36 mg. per 100 cc. The van den Bergh reaction was biphasic, with a serum bilirubin of 9.2 mg. per 100 cc. The prothrombin time was normal.

The urine was normal, except for a + test for bile pigment. The stools were light brown, with a trace of bile pigment.

A roentgenogram of the gall bladder showed this organ to fill faintly with dye. There was no definite contraction after a fatty meal. The Graham test was considered positive.

On the fourth hospital day, duodenal drainage gave clear, dark green "A" and "C" specimens. No "B" bile could be obtained. After prolonged drainage, milky white bile was obtained from an uncertain locality. Crystals resembling calcium bilirubinate were found on microscopic examination of the bile obtained after the administration of magnesium sulfate.

The temperature continued to be normal. On the seventh hospital day, a laparotomy was performed. The liver appeared "diffusely scarred," suggesting "early cirrhosis." A large gall bladder, covered by tenuous omental adhesions, was removed. The common duct, dilated to a diameter of more than 2.5 cm., was opened, and freed of two pigment stones. The ampulla was subjected to dilatation and irrigation. A T tube was sutured into the common duct, and closure was effected, with drainage to subhepatic region. The pathological report was chronic cholecystitis and choledocholithiasis.

Postoperatively, there was elevation of temperature to 100°F., recurring for several days. Although considerable amounts of clear bile drained from the tube left in the common duct, the patient continued to be jaundiced. One week after operation, the serum bilirubin was 10.4 mg. per 100 cc., with a biphasic van den Bergh reaction. The blood chemical findings were otherwise essentially negative.

On the sixth postoperative day, roentgenograms showed that a Hippuran injection through the T tube filled the biliary tract well. The tract appeared distended. Two days later, a similar injection showed marked dilatation of the common duct, with two filling defects, suggesting stones,

at the lower end of this duct. There was extensive retrograde filling of the hepatic duct and of two irregular cavities in the liver suggesting abscesses.

By the twenty-fourth postoperative day, the serum bilirubin fell to 4.2 mg. per 100 cc., and there was only slight residual jaundice. The patient was discharged with the T tube still in place, draining an average of 300 cc. of bile a day.

*Final admission* (one month later). The patient had been followed in the Out Patient Department, and continued on "bile cocktails" and bile salts by mouth. Constant drainage from the tube was clear except on one occasion when there was a small amount of yellow granular sediment. After two weeks, drainage ceased, and the jaundice cleared entirely. Two weeks later, the tube came out of place during an examination with Hippuran, which showed the biliary tract still dilated, with no evidence of stones.

The patient was readmitted to the hospital because of sudden onset of vomiting and acute abdominal discomfort about four hours previously. After an hour and a half, the discomfort progressed to severe pain. During the next half hour, the patient had a severe chill. He vomited twice again, and was brought to the hospital.

On readmission, he again showed very slight jaundice. The scar of the laparotomy and drainage was well healed. The entire abdomen was distended, with tenderness and muscle spasm that were most marked in the right upper quadrant. Signs of peristalsis were absent. The heart and lungs were normal.

The temperature was 102°F., the pulse 130, and the respirations 18. The blood pressure was 140 systolic, 90 diastolic.

Examination of the blood showed a white-cell count of 13,600 with 88 per cent polymorphonuclears and 4 per cent band forms, and a red-cell count of 5,680,000 with 105 per cent hemoglobin. The urine showed a + test for albumin, and a ++ test for bile pigment. The stools were positive for bile pigment and for occult blood. A Miller-Abbott tube was passed as far as the pylorus, but could not be manipulated past this point. Clyses of glucose were given. The patient's temperature fell to normal, rising to 101°F. on the third hospital day. On the fourth hospital day, an operation was performed.

#### DIFFERENTIAL DIAGNOSIS

DR. ARTHUR W. ALLEN: This is a long and complicated story. Is there anyone to demonstrate the x-ray films?

DR. TRACY B. MALLORY: We have the films, but no radiologist is here to interpret them. Perhaps Dr. Hamlin can help.

DR. ALLEN: Where are the cavities that were thought to be abscesses?

DR. EDWARD HAMLIN, JR.: There is tremendous dilatation of the entire biliary tree, especially the intrahepatic portion. The stones lie close to the ampulla. I was never certain about the abscesses.

DR. ALLEN: Are they consistent with the size of the stones removed?

DR. HAMLIN: They are smaller.

DR. ALLEN: At the age of eighteen, the patient had some very serious illness associated with fever and chills and jaundice that lasted for six months and during which his temperature for over a month was about 105°F. During this illness, he had edema, which might very well have been and probably was nutritional edema, because he had been ill a long while. Bloody stools were very probably the result of vitamin K deficiency, which accompanies jaundice of long duration. What that disease was, I do not know. Perhaps one can simply call it severe catarrhal jaundice, or hepatitis, and it probably was not associated with any mechanical obstruction to the extrahepatic ducts. It may have been some generalized disease affecting the liver secondarily. The patient apparently got along well for quite a while after this, and for sixteen years was without complaints. Then he began to have difficulty associated with gas on the stomach, and pain. The description is not too good, but it is probably good enough for me to say that ten years before admission the acute attack described was one of gallstone colic. The patient had indigestion and pain followed by jaundice. This responded well to morphine as pain of this sort does, in spite of all the scientific evidence that morphine causes a constriction of the papilla of Vater and therefore increases the pain and that one should use vasodilators instead. Every practitioner of medicine knows that morphine is the only drug that does these patients any good. The number of cases of the spasm type of pain that are relieved by antispasmodic drugs are very few, but the pain occasionally does respond to such medication, which, perhaps, should always be tried first. Usually, a real case of gallstone colic requires morphine for relief, and a large dose of morphine at that. The fact that this patient was suddenly relieved of pain when he vomited bile is interesting because, with the passage of a common-duct stone, the duodenum may suddenly be flooded with bile, which may be vomited. The morphine that was given for relief might have produced the nausea, but pressure within the common duct could account for it. I do not believe that we have to assume that the common duct perforated into the duodenum at that time, although this does rarely occur. The course was quite uneventful for nearly

seven years after that episode, with only occasional attacks of discomfort that a great many people with gallstones have and live with by dietary measures and accommodation of their mode of living.

Four days before admission, the patient had a strenuous time, apparently, following his trip in the country and began to have severe discomfort. Frequently, gallstone attacks are precipitated by motor trips. Any number of patients will tell you that such trips, as well as fatigue, produce an attack similar to that produced by indiscretion in diet. With the attack, this patient again had a chill, which began just before admission and which I suppose was the typical fever and chill of Charcot that is associated with inflammation in the bile ducts and is nearly always caused by stones.

The positive Murphy sign interested me. I asked a dozen or more students what the Murphy sign was; they did not know, and I meant to look it up but did not have time to do so. Apparently it is described here as tenderness in the epigastrium. I am familiar with Dever's sign, used by the late Dr. Charles A. Porter, which is associated with discomfort on heavy percussion over the right lower chest to indicate disease in or about the liver.

The blood count shows that the patient did not have very much infection at the time he was admitted. The Graham test was said to be positive, although no diagnosis of gallstones was made. The duodenal drainage is interesting in that crystals of calcium bilirubinate were obtained. We are not sure how reliable such a test is. When it is negative, one sometimes finds stones in the common duct, and when it is positive, one sometimes fails to find them. But when the experience has been accumulated, as it will eventually be, we can tell whether it is a 40 to 60 or a 30 to 70 chance. In this case, the test was positive, and stones were removed from the duct. The question arises about the white bile that was obtained and was said to be milky in appearance. It might be that the gall bladder was completely shut off by an old inflammatory constriction and that white bile was present within it. White bile rarely occurs in the common duct. We know that this man did not have a common duct full of white bile because they recovered green bile in the other two specimens. If this was white bile, it must have come from the gall bladder, and it was unusual that they could get it to drain, because one usually finds white bile when the cystic duct is completely occluded; this means that the bile has remained in the gall bladder long enough to have the pigment absorbed. How many weeks

that takes, I do not know, but it probably takes quite a long while.

At operation, the liver was found diffusely scarred, suggesting early cirrhosis. I should think that any person who had been through what this man had twenty-six years before in the way of hepatic fever might very well be expected to have a liver that would appear grossly abnormal.

A large gall bladder covered with adhesions was removed. The record does not say whether the bladder contained white bile or not. The common duct was dilated to a diameter of more than 2.5 cm., a very large common duct, and two pigment stones were removed. We do not know whether these were irregular, very dark biliverdin stones, or bilirubinate stones, which are lighter in color, or yellow cholesterol stones. Perhaps it is not important, but I should expect that they were the biliverdin type because these are much more apt to get stuck in the common duct since they are so sharp, hard and irregular. The ampulla was dilated, and a T tube was placed in the common duct. If one has such a problem and finds that the common duct is 10 mm. in diameter, the right hepatic duct will be about 7 mm., and the left slightly smaller—about 5 mm.; therefore, if one is going to dilate the opening into the duodenum so that the stones can pass that have been pushed back or remain in the liver duct,—and I am sure this happens quite frequently,—one must gently stretch the outlet to a size slightly larger than the diameter of the right hepatic duct. One can measure the ducts accurately with instruments, and if one makes the outlet slightly larger than the right hepatic duct, stones that are overlooked are apt to pass through. We have collected stones from the stools in such cases.

At any rate, this man did well after the operation. The record mentions a fever of 100°F. for a while, and states that jaundice continued for a week or so and that the van den Bergh reaction was higher than that on admission. Decompression of the common duct does relieve jaundice, but it relieves it slowly. It takes just as many days or weeks for jaundice to clear up following decompression of the liver as it does for the patient to acquire the jaundice. If he has been jaundiced for three months, it will require about three months to lose all signs of icterus. This slow recovery does not bother me too much. Possibly, the fever and the increased van den Bergh reaction were indicative of a slight, temporary, acute hepatitis precipitated by this operative maneuver, and I think one might assume that such a hepatitis took place.

The Hippuran injection is interesting in that it shows beyond the T tube two opaque bodies

or areas that could very well be stones in the common duct. A great deal of work has been done on the Hippuran injection of the biliary tree, and many surgeons have advocated performing this test on the operating table. Dr. Charles G. Mixer, who has a good setup for such examinations at the Beth Israel Hospital, believes that it saves re-exploration of many ducts. Mirizzi,<sup>1</sup> of Cordoba, Argentina, has written an excellent monograph on this procedure; he describes many cases in which second operations have been avoided by Hippuran injection done before the patient left the operating table. Our experience in this procedure has not been particularly good. In one case recently,—in which we knew that the patient should have another stone, since we had counted them before and could not find the last one,—we did a Hippuran injection in the operating room; the x-ray plate showed the duct all clear, the dye going into the duodenum without incident, but a week later, when we repeated the test, there was the stone outlined beyond the T tube just as clearly as these two shadows shown here. The stone may hide itself in the liver ducts and then may come down with the current of bile without passing through the papilla of Vater. I suspect that is what took place in this case. It may be a mysterious and peculiar situation, but as the history is given, I believe that that is what this man had. I do not believe he had any of the bizarre or peculiar situations that sometimes produce symptoms and signs that are similar to those of common-duct stones.

I believe that the second admission was probably due to bile peritonitis. The patient had lost the T tube two weeks before he came back. His last illness was precipitated by a very sudden onset of discomfort, and on examination with the stethoscope he was found to have a silent abdomen. Since the T tube had come out of the duct and the external wound had thoroughly healed, one could visualize that, with stoppage in the common duct due to stone in the region of the papilla, the patient might well have opened up the old incision in the common duct and developed a bile peritonitis. It is obvious that intestinal obstruction was considered, because a Miller-Abbott tube was passed. It is quite possible that the patient had something else to explain this very acute upset that brought him back to the hospital, but it certainly suggests bile peritonitis.

Bile peritonitis is quite a dangerous condition, and in 18 cases that we have had in this hospital in a period of ten years, the mortality was 22 per cent.<sup>2</sup> That is lower than it is in most clinics. McLaughlin<sup>3</sup> has recently published an article on bile peritonitis and collected what he could from

the literature on the subject. His mortality percentage ranged between 40 and 60 in various hospitals. In this clinic, it is low because we have learned that early recognition and early operation are indicated.

This man survived whatever this acute episode was for four days and was reoperated on; I should expect to hear that bile peritonitis was found at this operation and that very probably they were able to remove more stones from the common duct when they explored it.

Dr. HAMILIN: I operated at the first operation. Dr. Allen has described exactly what the situation was, and the subsequent events. At operation we found a very large common duct. We could palpate the stone close to the ampulla. After we had opened the common duct, we explored the hepatic ducts before we took out the obvious stones, to obviate the loss of stones above. We found none. We took out the two stones, dilating the ampulla, but probably not enough. The patient seemed to be doing well until the illness described took place. I did not see him on the second admission, except when he was operated on, and at that time the surgeon opened into a large abscess cavity of bile peritonitis, which was apparently rather tightly walled off. The surgeon believed that the patient was too ill for the common duct to be explored at that time. Drains were put in the abscess cavity, and for two or three days he was quite well and his drainage decreased very much, although he did have some bile in the stools and in the intestinal contents. He finally developed a hepatorenal syndrome, and died in apparent renal failure.

Dr. ALLEN: This is interesting because it is very difficult to prevent an external biliary fistula. An external fistula will break through the incision even if it is two or three weeks old, or bile will come through an old drainage tract, in almost every case. The Medical Service studied an interesting patient about six months ago—a woman who had had a cholecystectomy elsewhere shortly after delivery of her first child. She was about twenty-three years of age. She did badly after the operation and was re-explored in the hospital where she had had the original operation, and at this time they made a new incision. Both these incisions healed; the patient still did badly and after three months came to this hospital with a tremendously swollen abdomen. She had fluid in the abdomen, jaundice and a very high prothrombin level, and when they tapped her abdomen they obtained bile. When we explored her, we found that the common duct was communicating with a huge false sac, which filled almost the whole peritoneal cavity. We were able to pick up the proximal end

of the common duct and re-establish continuity with the intestinal tract. It is very unusual for anyone to survive confined bile leakage for such a long time. In every other case, in my experience, in which the patient has survived any length of time, bile has forced its way to the surface through the old drainage tract or through the incision.

#### CLINICAL DIAGNOSIS

Common-duct stone, with obstruction and probable bile peritonitis.

#### DR. ALLEN'S DIAGNOSES

Choledocholithiasis.  
Cholangitis.  
Bile peritonitis.

#### ANATOMICAL DIAGNOSES

Choledocholithiasis (intrahepatic).  
Cholangiectasis.  
Biliary cirrhosis.  
Focal acute hepatitis.  
Bile peritonitis.  
Chronic pancreatitis, with fat necrosis.  
Pulmonary infarcts, bilateral.  
Icterus.  
Bile nephrosis, slight.

#### PATHOLOGICAL DISCUSSION

DR. MALLORY: At autopsy, an extensive bile peritonitis was found. We were unable to demonstrate any actual communication between the peritoneal cavity and the biliary-tract system. Undoubtedly, a fistula must have been present, but it had apparently more or less closed off and certainly was not widely patent at the time of autopsy. The common duct did not contain any stones. However, in the duodenum just beyond the papilla we found a stone that we may have forced out of the common duct in manipulating the tissues. In contrast, when we followed the ducts up into the liver, we found the biliary radicles enormously dilated, as one sees in the x-ray film, and many stones within them, more than a dozen. The remainder of the liver was scarred and tough, and showed an unusually severe grade of biliary cirrhosis. In fact, I cannot remember having seen a liver in which there was so much collagen surrounding the bile ducts. In a localized part of the liver, there was also acute infection of the smaller bile ducts, many polymorphonuclears and some organisms being visible in the sections. So that there was a localized acute hepatitis, as well as old chronic biliary cirrhosis, but no gross abscess.

It is interesting, when one considers the death from apparent uremia, that the kidneys showed

virtually nothing. There was, as there always is, a slight degeneration of the tubules, so-called "bile nephrosis," which is invariable with chronic jaundice, but it is difficult to see how that per se would affect function of the kidney. I should be inclined to consider this primarily a case of liver failure rather than one of renal failure.

DR. ALLEN: I wish someone would tell me what the disease was that the patient had at the age of eighteen when he was ill for six months.

DR. MALLORY: There was nothing at autopsy by which we could say. It is conceivable that it was cholecystitis and cholangitis even at that time, since the fibrosis within the liver was so extremely dense and old.

DR. JAMES A. HALSTED: Do you think that it could have been typhoid fever, with localization in the gall bladder and subsequent formation of stones?

DR. MALLORY: That is conceivable. The gall bladder was not cultured at the time of the first operation.

#### REFERENCES

1. Mirizzi, P. L. *Litiasis del Coledoco. Tratamiento*. Buenos Aires A. Guidi Buffarini, 1939.
2. Allen, A. W., and Wallace, R. H. Drainage of the common hepatic duct: with special reference to bile peritonitis, wound infection and so forth. *Surg., Gynec. & Obst.* (in press).
3. McLaughlin, C. W., Jr. Bile peritonitis. *Ann. Surg.* 115:240-249, 1942.

#### CASE 28122

#### PRESENTATION OF CASE

A forty-six-year-old Greek leather worker was admitted to the hospital because of pain in the left knee.

The patient was well until nine months before entry, when he noted pain and swelling in his left knee that became gradually severer. The pain was most marked over the sides of the knee. There was little limitation of motion until two weeks before entry, when the knee became stiff, interfering with walking. There were no chills, fever or other symptoms, except slight malaise.

The past history was irrelevant. The patient had never had gonorrhea.

On admission, the patient appeared swarthy, heavy-set and in no acute distress. The left knee was swollen and hot. A mottled, brownish skin discoloration over the knee suggested previous application of heat. There was tenderness over the medial and lateral tibiofemoral fossas, more marked over the medial. The knee was held in 15 to 20° flexion, and only 5 to 10° more flexion was possible without extreme pain. The patella was not ballotable, but there was questionable fluctuation of the soft parts at each side of it. A lymph node 3 cm. in diameter was palpable in

the left groin, and one about 2 cm. in diameter in the right groin, neither being tender. There were no other positive physical findings.

The temperature was 99°F., the pulse 80, and the respirations 20. The blood pressure was 130 systolic, 90 diastolic.

Examination of the blood showed a red-cell count of 4,480,000 with 13.2 gm. hemoglobin, and a white-cell count of 5200 with 61 per cent polymorphonuclears. The blood Hinton reaction was negative on two occasions. The sedimentation rate was within normal limits. The urine was normal. A skin tuberculin test was performed, but the result was not recorded on the chart.

Roentgenograms of the left knee showed a finely granular area of calcification along the lateral margin of the right knee joint close to the region of the capsule, but extending downward and backward to the head of the fibula. There was indefinite follicular calcification just above the head of the fibula in the lateral view. There was a small amount of fluid in the upper recess of the knee joint. An area of diminished density 1 cm. in diameter appeared in the medial portion of the tibial eminence. No definite soft-tissue mass was seen.

Aspiration of the knee joint gave slightly cloudy, orange synovial fluid, with a viscosity of 9.9 and a normal mucin content. The fluid contained 11,550 red cells and 1150 white cells per cubic millimeter, with 6 per cent polymorphonuclears, 62 per cent monocytes, 22 per cent lymphocytes and 10 per cent clasmotocytes.

On the fifth hospital day, an operation was performed.

#### DIFFERENTIAL DIAGNOSIS

DR. CLAUDE E. WELCH: It appears that stiffness of the knee rather than pain was the factor that brought this patient into the hospital. There is no mention of any previous inflammatory lesions, such as boils, that would suggest a secondary inflammatory lesion of the bone.

It is of some interest that no distinct mass was palpable.

It is interesting that the men in charge considered it unnecessary to do other blood chemical studies.

May we see the x-ray films?

DR. GEORGE W. HOLMES: I can point out only the things that are indicated in the text—the area of calcification and the soft-tissue changes described. Here is the area of diminished density in the region of the tibial tubercle. In the lateral view, this area is not visible. The area of increased density in the soft tissue seems to lie posterior to the head of the tibia and below the fat

layer, in the muscular layer or in the margin of the capsule. It is important to know whether it is in the capsule or in the soft tissue just external to the capsule. I should say it was external, but that is a guess. In addition, there is some questionable thickening in the region just above the patella and a questionable increase in width of the joint space; this is suggestive of fluid, but there is no positive evidence of fluid. There is no bone atrophy, no evidence of spur formation about the condyles, nothing to suggest arthritis of the ordinary type, and nothing to suggest a chronic lesion like tuberculosis. So that from our point of view we have two things: an area of diminished density in the tibial tubercle, and an area of calcification in the soft tissues, neither of which I can explain.

DR. WELCH: I am interested that they term this spot "follicular calcification." Does that mean anything to you?

DR. HOLMES: It means that it was laid down in small flecks instead of masses.

DR. WELCH: I must admit that the findings of the aspirated knee-joint fluid mystified me, so that I asked one of our orthopedic experts about it. He said that he also was mystified, and we called the technician. I am not sure that I quote her correctly, but if I do, the fluid was thin, the normal mucin content being against arthritis. So far as the cell count is concerned, there is evidence against any type of septic joint, and that is as far as one is justified in going.

I shall mention the commonest lesions that may be expected in the knee joint and indicate the ones we can rule out. I have written them down in a more or less unclassified fashion. Could this be a metabolic disease, such as gout? There is no information, so far as the blood uric acid is concerned, and it is very unusual to have a single joint involved. Also, the history is not very typical. There were no severe paroxysms of pain. Could it be a Charcot's joint? Obviously not, according to the x-ray picture. Could it be tuberculosis? Dr. Holmes has remarked about the atypical features of the x-ray film so far as tuberculosis is concerned; clinically, this does not suggest a tuberculous joint, which usually appears in an old person and is very painful. Could it be any of the various specific forms of arthritis, such as infectious arthritis? That would be very unlikely, since the articular surface was essentially normal. Gonorrheal arthritis is excluded on the same basis. Could it be rheumatoid or hypertrophic arthritis of the joint? The x-ray picture is against it. We have nothing in the knee tap that would specifically suggest that diagnosis.



Could it be osteochondritis dissecans? I think we can eliminate that by the x-ray picture.

We are reduced, it seems to me, to two lesions: an inflammatory lesion of the nature of a Brodie's abscess that had not involved the knee joint, and some type of tumor located just below the synovial capsule. The calcification in the lateral margin of the knee joint, whether in the capsule or external to it, was there for a certain length of time,—no one knows how long,—and I do not believe that we have any definite right to say that this area of calcification is significant, although it is possible. Then, can we call this an inflammatory lesion or tumor? If inflammatory, it was an inflammatory lesion with no temperature, no elevated white-cell count, normal sedimentation rate, normal differential count and an aspirated fluid

diagnosis, and I shall say tumor of the knee; I do not care to be more specific concerning type.

DR. S. P. SARRIS: We had quite a discussion about this patient. A great many people looked at the x-ray films, and I discussed the case with most everyone in the X-ray Department and several members of the orthopedic and surgical staff. We were stumped for a diagnosis, and I consulted on this patient with Dr. Otto E. Aufranc, with the hope that between us we might be able to handle the surgical and orthopedic lesions of this area. I operated with the preoperative diagnosis of Brodie's abscess at the upper end of the femur. We had previous x-ray films, and it seemed to me that the area had increased since the first films were taken. Dr. Aufranc, I believe, favored the

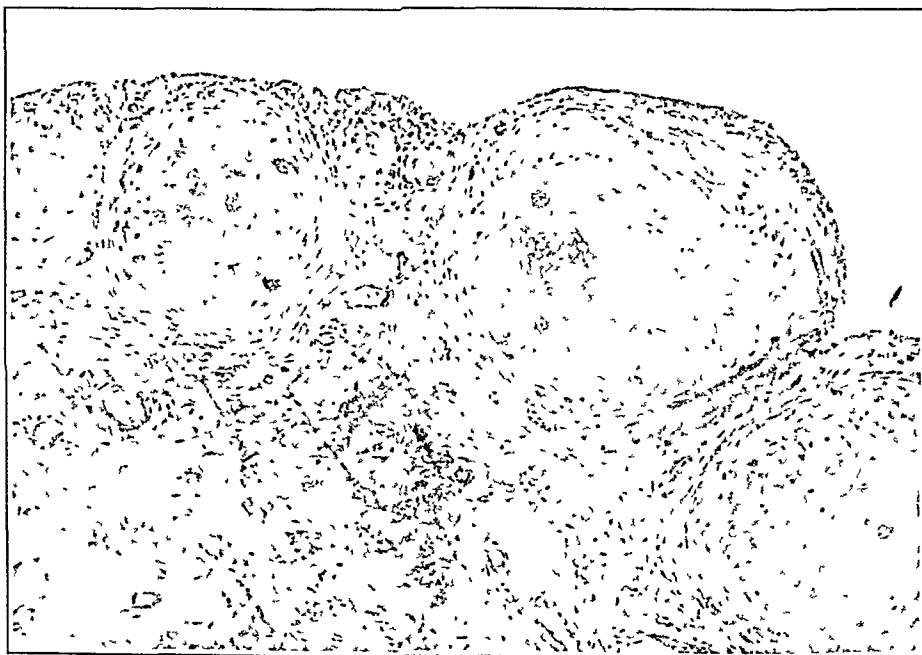


FIGURE 1. *Foci of Hyaline Cartilage Developing in the Synovia.*

that is not compatible. In other words, I am definitely inclined against the diagnosis of an inflammatory lesion, and I am inclined toward the diagnosis of tumor.

Suppose it is a tumor, what lesions could simulate this x-ray picture? That again is extremely difficult, because the x-ray film is not typical of any one of them. Primary tumors in that location are limited to osteogenic sarcoma of some type or synovioma, a primary tumor of the knee joint. The picture is not typical of a metastatic lesion except for the destruction of bone. It is hard to explain the area of calcification along the lateral margin of the joint on the latter basis.

It may seem that I have talked myself out of everything, but I must go on record as making one

diagnosis of aseptic necrosis of bone. At operation the knee joint was opened, and presented the strangest sight I have ever seen. It was packed with split-pea-sized pearly masses that were firm but also elastic. Many of them were completely free of attachment to any of the normal structures of the joint, whereas others were embedded in the synovia or attached to it by the pedicle. I estimated there was about 200 cc. of solid material. It was all removed, and a synovectomy was performed.

DR. WILLIAM B. BREED: When you finished the operation, what was your diagnosis?

DR. SARRIS: At that point, we still did not know what it was. We called over the pathologist, Dr. Walter Bauer and a few others, and

after seeing the knee joint open we still did not know what it was.

#### CLINICAL DIAGNOSIS

Traumatic synovitis, left knee.

DR. WELCH'S DIAGNOSIS

Tumor of the knee joint, unspecified.

#### ANATOMICAL DIAGNOSIS

Chondromatous metaplasia of the synovia of the knee joint.

#### PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: The joint, as Dr. Sarris has explained, was completely filled with gristly material that proved on microscopic examination to consist almost entirely of cartilage. The cartilaginous foci formed within the synovia, as one can see from the photomicrograph (Fig. 1). The synovial mesothelium is at the top of the picture, and one can see that immediately beneath it are multiple round masses of varying size, each of which is a little focus of hyaline cartilage. The deposits are of varying age, some of them obviously freshly formed, whereas others must have been present for a long time, since they are partially calcified. When these foci arise in the synovial villi, they hang by narrow pedicles into the joint cavity, frequently break off and become

joint mice. They continue to contain living cartilage cells. We have had one other case of this sort. In another possibly related case, the synovia was entirely replaced by chondrosarcoma, so that I suspect the cartilage can and occasionally does degenerate into malignant tumor. I should term the process chondromatous metaplasia of the synovia. There does not seem to be a great deal written about the condition, although Jones\* reported 19 cases in 1924 from the Mayo Clinic. Its etiology is entirely unknown.

A PHYSICIAN: Are you surprised that the x-ray film did not show more?

DR. HOLMES: One would not expect it to.

A PHYSICIAN: What is the prognosis?

DR. MALLORY: Perfectly favorable.

DR. HOLMES: How did you explain the area of diminished density?

DR. SARRIS: I was going to add that, at the time of the operation, there seemed to be a mass of these nodules pressed between the two joint surfaces overlying this area, and we interpreted it as aseptic necrosis from pressure atrophy.

DR. MALLORY: The only point on which the various consultants who saw this patient before operation agreed was that diagnosis was impossible without biopsy.

\*Jones, H. T. Loose body formation in synovial osteochondromatosis with special reference to the etiology and pathology. *J. Bone & Joint Surg.* 22:407-458, 1924. The histogenesis of cartilage as shown in chondromatosis of the knee joint. *Ibid.* 9:310-314, 1927.

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established In 1828

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND  
PUBLISHED UNDER THE JURISDICTION OF THE  
COMMITTEE ON PUBLICATIONS

Official Organ of  
THE MASSACHUSETTS MEDICAL SOCIETY  
and  
THE NEW HAMPSHIRE MEDICAL SOCIETY

## EDITORIAL BOARD

Joseph Garland, M.D.	Stephen Rushmore, M.D.
William B. Breed, M.D.	Henry R. Viets, M.D.
George R. Minor, M.D.	Robert M. Green, M.D.
Frank H. Lahey, M.D.	Charles C. Lund, M.D.
Shields Warren, M.D.	John F. Fulton, M.D.
George L. Tobey, Jr., M.D.	A. Warren Stearns, M.D.
C. Guy Lane, M.D.	Dwight O'Hara, M.D.
William A. Rogers, M.D.	Chester S. Keefer, M.D.

## ASSOCIATE EDITORS

Thomas H. Lanman, M.D.	Donald Munro, M.D.
Henry Jackson, Jr., M.D.	

Walter P. Bowers, M.D., EDITOR EMERITUS  
Robert N. Nye, M.D., MANAGING EDITOR  
Clara D. Davies, ASSISTANT EDITOR

SUBSCRIPTION TERMS. \$6.00 per year in advance, postage paid, for the United States (medical students, \$3.50 per year); Canada, \$7.04 per year, Boston funds; \$8.52 per year for all foreign countries belonging to the Postal Union.

MATERIAL for early publication should be received not later than noon on Friday.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston, Massachusetts.

## NEW LAMPS FOR OLD

SHORTLY after John Brown's ill-fated raid on Harper's Ferry, Henry Thoreau, impressed by that gallant fiasco, felt the need of doing something about it, of allying himself with a cause, no matter how fantastic, in whose spirit he believed. Against the advice of friends, he hired a hall, announced a mass meeting, and delivered an address in which he advanced the theory that we as a nation had used up our inherited liberties. Just as our other inheritances may eventually become depleted through taxation, dispersion and poor investment, so today, according to Thoreau's theory, we may again be said to have exhausted our stock of passively acquired freedom.

The Civil War was a crusade to reaffirm a nation's belief in democracy—in the viability of various bills of rights under which free people might live. This belief was reaffirmed in 1861 and is today once more undergoing a trial ordeal. This trial, to which we have been subjected for the last decade and which has reached its crucial period, concerns the fitness of a people to assume the obligations as well as to enjoy the benefits of their liberty.

Liberty, which is basically a spiritual thing, can be interpreted as a very material thing when the need for testing it has arisen. This shore was settled largely by people who sought spirituality, who strove for it, and who passed it on to their descendants. As the rich resources of the land came to the surface, the acquisition of wealth that could be chemically assayed became a universal goal, and liberty came to be interpreted as the right to acquire that wealth in unlimited quantities.

This inherited liberty is in its turn being used up, and a present generation must find its freedom, for it is surely losing the old. The day on which material goods are being destroyed, and the rate at which the wealth of a nation is being consumed, must make us acutely aware that the end of our present system of utilizing liberty is in sight, and that the era of passive exploitation is over.

The "American way of life" that we are fighting for must have a very different meaning from that which can be so easily read into the words of this phrase. If by the American way of life we mean the exploitation of the land for individual gain,—a universal and perpetual struggle in the pursuit of a dollar of easy virtue,—the American way of life is not only indefensible, it has already vanished around the corner. If, however, by the American way of life we mean the safeguarding to each of the opportunity to work out his own destiny, if we mean a personal and national adaptability that will see us through the profound changes that are to come, we are in a fair way to construct a new liberty for our generation.

## HOSPITAL FACILITIES

The Bureau of the Census of the Department of Commerce has recently released what it describes as "the most widespread survey ever made of hospital bed facilities in the United States."<sup>1</sup> In the release, figures are given for the year 1939, and they seem to be largely interpreted in terms of the "minimum requirements for adequate medical service," as set up in 1933 by the Committee on the Costs of Medical Care. The figures are then broken down into three groups according to the total number of beds per population unit for each state. Thus, four states, including Massachusetts, and the District of Columbia are said to have good facilities, and eighteen states to have adequate facilities; the remaining twenty-six are classified as having inadequate facilities.

Just what the Bureau means by the "most widespread survey ever made" is not clear. Six months previously, the American Medical Association<sup>2</sup> released its annual register of hospitals, listing at least 1,304,628 beds and bassinets (against the Bureau's stated 1,282,785 beds). The Bureau's release is also vitiated by its failure to consider its subject qualitatively. The only criterion used is the ratio of beds to population, and on this alone it passes judgment that more than half the states have inadequate hospital facilities. The Bureau implies that 2000 more 170-bed hospitals are needed in this country. This may appear necessary to some politicians, but of greater fundamental importance is the need for improving existing hospital facilities, so that more of the present beds can be approved by the American College of Surgeons and by the Council on Medical Education and Hospitals of the American Medical Association. This would mean not only a great increase in laboratories and equipment, but an even greater increase in trained man and woman power. The lack of quality and efficiency in hospitals is even greater than the lack of beds, and is less easily remedied. Of the hospital beds investigated by the American Medical Association, only a half were in hospitals approved by the American College of Surgeons and only a third were in hospitals ap-

proved for internships, residencies and fellowships by the American Medical Association.

If the Bureau of the Census is going into these matters, it appears that professional advice should be employed. It, of all governmental departments, should be up to the sixteenth (1940) census by now. The subject is too important to be discussed in any but the most enlightened and up-to-date manner. There is a war to win before the Nation returns to the political connivances of 1939.

## REFERENCES

- 1 Release 17608, September 18, 1941. Department of Commerce, Washington, D. C.
- 2 Hospital service in the United States *J. A. M. A.* 116:1055-1144, 1941.

## OBITUARY

### SOMA WEISS

1899-1942

Doctor Soma Weiss, Hersey Professor of the Theory and Practice of Physic at Harvard University and physician-in-chief of the Peter Bent Brigham Hospital, died suddenly on January 31, 1942, at his home in Cambridge, Massachusetts, aged forty-three years. Death was caused by a subarachnoid hemorrhage.

Doctor Weiss was born in Besterce, Hungary, on January 27, 1899, and came to the United States in 1920. Early in life, he showed great interest in scientific research and, while attending the Royal Hungarian University in Budapest, received the appointment of demonstrator and research fellow in physiology and biochemistry. This interest in fundamental research continued in an uninterrupted manner. In 1920, he became an assistant in pharmacology at Cornell University, and during this period, he made fundamental observations on the mechanism of vomiting and the action of digitalis. In 1921, he received his Bachelor of Arts degree from Columbia University, and two years later, graduated from Cornell University Medical School. Following an internship at Bellevue Hospital, New York City, he joined the Department of Medicine of Harvard Medical School as a member of the staff of the Thorndike Memorial Laboratory of the Boston City Hospital, at first under the direction of Dr. Francis W. Peabody and later under that of Dr. George R. Minot. While associated with the Boston City Hospital, he became assistant director of the Thorndike Memorial Laboratory and, later, director of the Second and Fourth Medical Services and chief of the Fourth Medical Service. He remained there

until 1938, when he was appointed physician-in-chief to the Peter Bent Brigham Hospital and Hersey Professor of the Theory and Practice of Physic at Harvard University.

Doctor Weiss was a member of many medical and scientific societies, including the American Society for Clinical Investigation, Association of American Physicians, American Heart Association, American Academy of Arts and Sciences and American College of Physicians. He was a member of the Council on Pharmacy and Chemistry of the American Medical Association, and took an active interest in the Massachusetts Medical Society and in many problems concerned with national defense.

His interests in medicine were extremely broad, but he was especially well known for his work in cardiovascular disease and in clinical pharmacology and therapeutics. Starting with a study of the velocity of blood flow with Dr. Herrman L. Blumgart, he devoted his attention to such problems as hypertension, carotid-sinus disorders, syncope, shock, beriberi, heart disease and chronic pyelonephritis. Shortly before his death, he published, with Dr. Lewis Dexter, a monograph entitled *Toxemias of Pregnancy*. All his writings reflected his interest in seeking the truth, which led him into a careful and patient search for scientific facts concerning the problem at hand. He was always subjecting his ideas and thoughts to investigation and experiment. Problems that were constantly arising on the wards were transported to the laboratory for solution. "How" and "why" were two words that he used frequently in the discussion of medical problems.

He had a number of pupils who now hold important posts in academic medicine in this country and abroad. His guidance and stimulus were an invaluable asset to them.

Here was a man with a profound knowledge of medicine, a keen sense of humor and the courage of his convictions, combined with a great kindness and consideration of others. The memory of Soma Weiss and his achievements will always remain in our hearts and in the record of his short but striking and productive career. As Tennyson remarked, "Tho much is taken, much abides."

C. S. K.

## MEDICAL EPONYM

### DE MUSSET SIGN

The de Musset sign of aortic regurgitation was described, not by a physician, but by Paul de Musset (1804-1880), brother of the poet, in his *Biog-*

*raphie de Alfred de Musset; sa vie et ses oeuvres* [Biography of Alfred de Musset: His life and his works] (Paris, 1877). The following translation is from pages 274 and 275:

The illness so well cared for by Sister Marcelline had left him with a troublesome tendency to affections of the chest. . . . We called the doctors twice during the course of the winter; they bled him too often.

Whatever they may say, I am convinced that their lancets caused him irreparable harm. At breakfast one morning in March, I noticed that my brother's head was bobbing involuntarily with each pulse beat. He asked my mother and me why we were looking at him with such a startled air. We told him what we saw, and he said, "I did not think you could see it; but I will reassure you."

He made some sort of pressure on his neck with his index finger and thumb, and in a moment his head stopped marking his pulse. "You see," he then said to us, "that this dreadful illness can be cured by simple and inexpensive means."

We were reassured, being ignorant, for we had just observed the first symptom of a grave malady to which he was to succumb fifteen years later.

R. W. B.

## MASSACHUSETTS MEDICAL SOCIETY

### COMMITTEE ON MATERNAL WELFARE

CASE HISTORY: ABLATIO PLACENTAE,  
ASSOCIATED WITH HYSTERECTOMY AND  
FOLLOWED BY DEATH

A twenty-four-year-old para III was admitted to the hospital with a diagnosis of ablatio placentae. The past history was irrelevant. The two previous pregnancies had been terminated by cesarean section, the reason for the first section not being known.

The patient had had no prenatal care except for one visit to a physician at the beginning of the eighth month. When nearly at term, she began to bleed and summoned her physician, who made the diagnosis of internal concealed hemorrhage and immediately sent her into the hospital. Her condition on arrival suggested severe intrauterine hemorrhage. The uterus was firm, the fetal heart was not audible, and the patient was not in labor. Soon after admission, the vagina was packed with gauze. External bleeding became profuse. Two thousand cubic centimeters of 10 per cent glucose was administered intravenously, and was followed by transfusions totaling 3000 cc. of citrated blood. In spite of these measures, external bleeding continued, and a laparotomy was performed seven hours after the patient entered the hospital. The fetus and uterus were removed. The day following operation, the patient became

edematous, developed edema of the lungs, and died, presumably of cardiac failure

*Comment* Inadequate prenatal care may have been responsible for this death. There is no record of the findings when the patient was seen once at the beginning of the eighth month. It is probable that had she been seen again after this visit, increased blood pressure and albuminuria would have been recognized. In view of the two previous cesarean sections, unless this patient was practically moribund when she entered the hospital, it is likely that a laparotomy immediately on entrance, preceded by transfusion, would have averted this catastrophe.

The generalized and pulmonary edema that appeared the day after operation may well have been caused by the tremendous amount of fluid that this patient hid. If not, the edema and cardiac failure were due to the cardiac asthma so frequently seen in crises of toxic separation of the placenta. If the patient's condition on arrival was so serious that laparotomy was contraindicated and conservatism seemed the only intelligent treatment, the cervix as well as the vagina should have been picked and a Spanish windlass applied. This method should have been adopted only as a last resort, with the knowledge that rupture of the uterus from the previous cesarean sections was always possible.

The record does not state that the hysterectomy following the cesarean was necessitated by a uterus that would not contract. This does happen in patients with a completely separated placenta, and the only way to control the bleeding is to remove the uterus. On the other hand, if it is not imperative to remove the uterus in a patient in such poor condition, hysterectomy is certainly a more serious operation than cesarean section and hence is contraindicated.

#### THE ROLE OF THE MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH IN CIVILIAN DEFENSE\*

Recently, several persons have asked me what part the Massachusetts Department of Public Health plays in the National Defense Program. They went on to say that although they have frequently read and heard about the plans of other agencies, they have rarely come across any mention of the Department of Public Health.

The answer to this is that the Department of Public Health as part of its everyday duty, must always be prepared to deal with emergencies that may affect the public health such as epidemics, floods and hurricanes. Being always prepared for emergencies, I suppose we have more or less taken it for granted that the public would realize our effective participation in the defense program.

Twice within the past ten years, we have been called

on to function in times of disaster of natural origin. The flood of 1936 in the Connecticut and Merrimack valleys and the hurricane and flood of 1938 are still fresh within the memories of all of us, although their magnitude and importance pale when compared with the enormity of the present problem. In both emergencies, the facilities of the department were readily made available to the distressed areas. In general it may be said that in the present crisis we shall function according to a state plan, which was drawn up after the flood of 1936 and revamped in 1940 to include all state and allied agencies that must be called on to render aid during any major emergency.

It can be considered that the Department of Public Health has two parts to play in the present defense effort. The first, and perhaps the more dramatic part, is our role in the State Emergency Plan. On receipt of official notification of a possible disaster, the specialized personnel in the Massachusetts Department of Public Health report for duty at their assigned stations. On this official notification, many of our workers will report to various armories throughout the State, where they will function in close co-operation with the State Guard and various local organizations. The department is providing for two first aid rooms in the State House for the care of State House personnel in time of disaster.

Our principal problem is to maintain public health practices at the highest possible level of efficiency, for it is in times of disaster that such practices are most seriously threatened. Our staff members, through the various armories, are readily available to render advice, guidance and assistance in the many public health problems that may arise. For example, the engineers may be asked to assist in a matter concerned with water supplies or sewage disposal. Military catastrophes of one type or another are quite apt to have a damaging effect on water supplies and sewage disposal systems. Modern sanitary engineering has been perfected and developed so that in our time typhoid fever and other intestinal infections have been reduced practically to a minimum. Any interference with these systems must be instantly coped with and for this reason our state engineers have staffed their field personnel in even smaller districts than the other divisions have.

If pollution of a water supply should occur, engineers would be immediately on hand to assist the water boards and water companies in taking whatever steps are necessary to render the water supply safe. Emergency chlorine and chlorinator depots are distributed strategically throughout the State to supplement the reserves of local communities. Engineers and inspectors are ready to assist in obtaining specimens for laboratory examinations to ascertain whether or not the water supply is safe. We have obtained the co-operation of local laboratories for emergency examination of such specimens in case it is impossible to forward them to the departmental laboratory.

Similarly, the engineers, together with the co-operating local agencies, are prepared to remedy disruptions in the sewage systems, since these disruptions may result in the pollution of water supplies and consequently in the possible spread of disease.

Our district health officers will undoubtedly be asked to co-operate in ascertaining whether or not epidemic conditions exist or threaten and, if so, how they can be brought under control. They may be asked to help in ruling out communicable diseases among possible evacuees and frequently in emergencies are asked whether or not preventive inoculations of one type or another are indicated.

Our supervisor nurses will be available to local health departments and visiting nurse associations in meeting

\* A. Green gives to Health broadcast given through Station WAAF by Dr. Paul J. Jakubczak on Saturday, January 17, and sponsored by the Public Health Council of the Massachusetts Medical Society and the Massachusetts Department of Public Health.

the problems of carrying out a generalized program under extremely difficult conditions.

Our nutritionists will be acquainted with the whereabouts of reserve food supplies and are skilled in such things as emergency feedings and the mechanics of setting up canteens.

Food inspectors and sanitary officers are always in demand to pass on whether this food can be used or that food should be condemned. Laboratories are distributed throughout the State in such a way that it can be immediately learned whether or not milk or food has been endangered by possible contamination.

Our medical social workers will undoubtedly be asked to bring to bear their comprehensive knowledge of community resources and of how they can be marshaled to effect a solution in any particular emergency.

It can readily be seen that to have units established in certain key armories will facilitate bringing to any part of the State the entire services of the Department of Public Health with a minimum of delay. From time to time, it is possible that certain key individuals might be released from armory assignments to work with other agencies in meeting particular problems that may arise. We must remember, however, that the first duty of the department is to make it possible for state services to reach into all corners of the State. We cannot limit our plans to any particular city or district. Every possible effort is being expended for the closest co-operation between our personnel and the splendid and comprehensive program worked out for this particular emergency by the Committee on Public Safety. For example, our State district health officers, of whom there are eight and who act as the official representatives of the Commissioner in their districts, have been designated by the committee on public safety as regional directors for health. In this respect, they have been of assistance in the formation of many local city or town committees, and have also assisted such committees in developing the desired program.

Our division directors keep in close touch with the policies and plans of the various subcommittees of the Massachusetts Committee on Public Safety, particularly those dealing with health and sanitation. In this way, the activities of our specialized personnel can be correlated and integrated with those of the state committees. Other members of our department are working in conjunction with the aforementioned committees on such things as emergency housing, evacuation hospitals and similar problems.

What I have said thus far constitutes our first role in national defense. I should like to dwell a few moments on our second role, which, although it may be less dramatic, is nonetheless significant. The so-called "home front" is always of importance in war, but particularly is this true at the present time. It is universally admitted that a continued uninterrupted flow of ships, tanks, planes and guns from the shipyards, arsenals and factories is an absolute necessity in the successful conduct of this war. That this stress of production may be uninterrupted, the public health must be kept at an unusually high level. It is at times such as this, when all are more or less overfatigued and continually busy about other things, that health may be allowed to become impaired. We must be on our guard to keep "sound minds in sound bodies." The children of today are the men of tomorrow, and the men of tomorrow are quite apt to be soldiers. We must profit by the lessons learned in the recent draft and put into effect all possible measures that will cause young men to appear before the Selective Service boards in the

best physical condition. Similarly, the health of workers in industry must be protected and preserved, lest fatigue, malnutrition, respiratory disease or other disease be allowed to decimate industrial ranks and seriously interfere with production.

During the anxious days ahead, we must continue to throw every protection and safeguard about women and children. From a health point of view, no effort must be relaxed toward keeping our communities safe. Health-education measures designed to promote better nutrition must go on. The conditions of war, overcrowding, hunger and exposure, although fortunately not prevalent in this state, must be anticipated. Such conditions are the forerunners of epidemics. Because disease itself is absent from our midst at the present time does not mean that the bacterial causes are not always present, awaiting only suitable soil.

The second role that the Department of Public Health plays, then, is this critical one of making absolutely certain that the ground gained in the war against disease is not lost in the present crisis. Even though we were absolutely safe from bombing and sabotage, I should consider this maintaining of the public health to be an extremely vital assignment. This is, of course, not the responsibility of the Department of Public Health alone. Each local board of health is alert to the responsibilities, and plans to carry on in the future as in the past. The voluntary agencies are likewise mindful of their responsibility, and I can assure you that through the co-operative effort of all concerned, health standards will be maintained.

I shall now summarize briefly the dual role of the Massachusetts Department of Public Health in national defense. In the first place, it is prepared to bring to bear in any affected area in the State specialized personnel equipped and capable to cope with any situation. Such personnel will function out of certain key armories in close co-operation with the State Guard, local civilian-defense committees and local health departments. Secondly, it is alert to the need of maintaining health standards even in the absence of air raids and sabotage, and is gearing its efforts to cope with this very real, if less dramatic, duty.

## DEATH

LADD — MAYNARD LADD, M.D., formerly of Boston, died March 9. He was in his seventieth year.

Born in Romeo, Michigan, Dr. Ladd received his degree from Harvard Medical School in 1898. He was formerly a member of the faculty of Harvard Medical School, director of the preventive clinic at Boston City Hospital, chief of the children's department of the Boston Dispensary and president of the American Pediatric Society.

He is survived by two daughters.

## WAR ACTIVITIES

### CIVILIAN DEFENSE

#### NURSING SERVICE FOR THE WAR

Nursing service is being rapidly organized to take its place in the civilian-defense program. A full-time nursing consultant is on duty as a member of the staff of the Medical Division of the Office of Civilian Defense in Washington, and the Subcommittee on Nursing of the

Health and Medical Committee of the Office of Defense Health and Welfare Services also serves as the Nursing Advisory Committee of the Office of Civilian Defense. Through the consultant and the advisory committee the Medical Division is in contact with all federal agencies that have nursing programs and the Nursing Council on National Defense, which represents national nursing organizations, the Red Cross and federal agencies. To assist the regional civilian-defense offices in interpreting the emergency medical service program, field nursing consultants of the United States Public Health Service, the United States Children's Bureau and the American Red Cross have been made available for consultation. One nurse representing the Red Cross and another representing one of the other two agencies have been assigned to each state.

The most recent development in the nursing program is the establishment of state nursing councils. These councils are made up of representatives of nursing organizations, official agencies with nursing programs and the Red Cross. It has been recommended by the Medical Division of the Office of Civilian Defense that the services of these state councils be made available to state defense organizations.

Nursing representation on local medical advisory councils has also been recommended by the Medical Division of the Office of Civilian Defense, and local nursing councils are being formed throughout the country.

Nurses are required in the emergency medical service now being developed by the Medical Division of the Office of Civilian Defense. They will be needed not only for the care of casualties in hospitals but for service with medical first aid posts. If it is necessary to discharge patients from hospitals earlier than usual to make room for war casualties nursing service may be necessary for such patients in their homes. For this purpose, the organizations in the community having public health nurses will co-operate in meeting the needs for providing home care. Nurses will also be required for service in base hospitals, to be established in protected rural areas if needed for the reception of civilian casualties due to enemy action.

Other phases of the work of nurses in civilian defense are the training programs now being carried out in collaboration with the Red Cross. Both the Office of Civilian Defense and the Red Cross are urging promotion of the nurses aide program. One hundred thousand must be trained in the next few months to assist nurses in casualty receiving hospitals and in field casualty services. Nurses are being urged by the Medical Division to arrange to teach home nursing courses, so that more women will be ready to care for sickness in their own homes during an emergency and relieve the hospitals of some of their load. Nurses are also asked to take Red Cross first aid courses so that they may be prepared to help in casualty services and also to qualify as instructors for first aid courses.

and observation at the bedside. The influence of the nervous system on functional and organic somatic disturbances is not a recent psychiatric discovery. It has been known for decades that certain psychic and emotional states are the sole cause of general and local functional disorders, and quite often exciting causes in organic affections. An emotional upset quite frequently precipitates an attack or intensifies the symptoms of gallstone colic or of angina pectoris. In the latter condition it is as potent a factor as physical exertion. But the essential causes of these diseases are the structural changes in the organs, and very few physicians would view them as psychiatric in origin. The same holds true regarding ulcerative colitis.

Mucous colitis is a comparatively rare affection, and spastic colitis, — or more accurately, a spastic colon, for there is hardly any colitis in this condition — a very common one, whereas ulcerative colitis is less frequent than the spastic colon and much more frequent than mucous colitis. Ulcerative colitis begins rather suddenly with blood and bloody mucus in the stools in some cases, it is preceded for a week or more by rather intense diarrhea, but in no case to my knowledge has there been any antecedence either of mucous colitis or of a spastic colon.

Ulcerative colitis is a chronic disease characterized by remissions and acute exacerbations, the remissions lasting from weeks to years. Patients with this affection have financial, economic and social worries and conflicts just as well as people with a normal colon. These worries and conflicts may be factors in acute exacerbations, but their absence, in my experience, is no factor in the remissions, which are due to the natural course of the disease and not to any psychiatric treatment per se. The personality of patients with this affection is, to my mind, about the same as that of persons with any other bodily disease or that of what we call normal people, although some colitis patients may well belong to the giver uppers. When a patient has about twelve to thirty evacuations, and rather painful ones, in twenty four hours, one would hardly expect him to be jovial and optimistic, and it would be rather surprising if he should not eventually become a 'giver upper'. Some clinicians maintain that there is no difference between the functional and the organic, and this is perhaps theoretically true. The concept of body mind has a strong philosophic appeal but the dualism of body and mind is eminently pragmatic, and there is at least some difference between multiple sclerosis and psychoneurosis accompanied by various organic disorders.

Ulcerative colitis is a severe organic disease characterized by remissions and exacerbations. Mental and emotional factors are of importance in its symptomatology, as they are in any other organic disease, but as to its being psychiatric in origin and pathogenesis this view, to my mind, is purely scholastic and a return to medieval mysticism.

LOUIS FISCHBLIN, M.D.

485 Commonwealth Avenue  
Boston

#### SEROLOGIC TESTS FOR SYPHILIS

*To the Editor* The necessity of serologic tests for syphilis as part of the examination of applicants for marriage licenses and the short time usually available to such applicants as are in military service is not infrequently subjecting the Wassermann Laboratory of this department to adverse criticism. We believe that a statement of the circumstances should demonstrate that such criticism is unjustified.

#### CORRESPONDENCE

##### PSYCHIATRIC ASPECTS OF ULCERATIVE COLITIS

*To the Editor* 'Psychiatric Aspects of Ulcerative Colitis' by Dr George E. Daniels in the January 29 issue of the Journal, is to my mind at variance with clinical experience



The performance of serologic tests for syphilis in a nonroutine manner, as is frequently requested for premarital examinations, is not feasible under the present laboratory setup. The very large number of routine tests (upward of 40,000 in January) throws such a burden on the facilities and personnel of the laboratory that it is not practicable to impose the additional burden of accepting specimens out of turn and testing them by nonroutine methods. Furthermore, it is unfair to accept such specimens at all unless the practice can be made general, and our physical facilities do not permit of expansion to carry such an added burden.

The rendering of reports by telephone, which is also requested frequently, would appear to be barred by the provisions of Section 119 of Chapter 111 of the General Laws, which provides that "... laboratory ... records pertaining to gonorrhea or syphilis shall not be public records, and the contents thereof shall not be divulged by any person having charge of or access to the same, except upon proper judicial order or to a person whose official duties, in the opinion of the commissioner, entitle him to receive information contained therein." As the purpose of this statute is to protect the individual, and as the laboratory has no way to identify the source of telephone calls, it would seem that reports can be sent to physicians only by mail or by a duly accredited messenger.

Authorization to perform premarital examinations was granted to medical officers of the United States Army, Navy and Public Health Service on active duty by Chapter 697 of the Acts of 1941; and all Army, Navy, Public Health Service and state health department laboratories were approved by the Public Health Council for the performance of the necessary serologic tests. It is suggested that physicians call these provisions to the attention of the prospective brides of men in military service, so that the latter will not delay their own examinations needlessly.

In further recognition of the fact that many times the circumstances of military service and so forth give applicants for marriage licenses only a short time in which to fulfill the requirements of the law, we have inquired of all laboratories approved for performing serologic tests for syphilis as to whether they wish to accept such specimens for rapid testing and what their fees are for such services. This information has been tabulated in the hope that it will prove of service to physicians.

The following laboratories will do rapid Hinton tests (and confirmatory tests when needed) for premarital purposes, at the charge indicated:

Boston Dispensary	\$3.00
Boston Health Department (Boston residents, only)	No charge
Brockton Health Department	
Brockton residents	No charge
Nonresidents of Brockton or nonresident physicians	\$3.00
Leary Laboratory, Boston	3.00
Massachusetts General Hospital	3.00
Mercy Hospital, Springfield	2.00
Peter Bent Brigham Hospital, Boston	3.00
Providence Hospital, Holyoke	2.00
St. Luke's Hospital, Pittsfield	1.00

PAUL J. JAKMAUH, M.D.  
*Commissioner of Public Health*

State House  
Boston

## REPORTS OF MEETINGS

### HARVARD MEDICAL SOCIETY

A regular meeting of the Harvard Medical Society was held at the Peter Bent Brigham Hospital on November 12, with Dr. Elliott C. Cutler presiding.

The case presented was that of a seventy-three-year-old man admitted after an alleged injury in an automobile accident. When first seen, the patient appeared to be in shock but was mentally clear, with a blood pressure of 90/60. He was given emergency treatment for shock. Physical examination revealed mobility and crepitus of the pelvic bones, an obvious fracture and tearing of all the ligaments of the right ankle, and a sprain of the right knee; neurologic examination was negative. After an hour, the chart showed that the general condition was good, and the patient was removed to the operating room, where, under Pentothal anesthesia, the fractures were reduced. Again, the blood pressure fell, and he was given intravenous saline solution, 25 gm. of human albumin and a small blood transfusion. Hematocrit readings were taken at the time and subsequently as an aid in following the course of the patient. The later course was essentially smooth except for an anemia, for which he received further transfusions.

In discussing the case, Dr. Carl Walter emphasized the age of the patient, the fractures of the leg and pelvis and the element of shock. The early treatment of the fractures and the shock is an aid toward a favorable outcome, especially in aged patients. In all fractures of the pelvis, the question of bladder injury arises, but there was no evidence of any in this case.

The speaker of the evening was Mr. Gordon Gordon-Taylor, surgeon to Middlesex Hospital, London, and Surgeon Rear Admiral to His Majesty's Navy, whose subject was "Certain Surgical Problems of Modern Warfare." Slides were shown of the building of the Royal College of Surgeons before and after the bombing of May 10 and 11 of this year, when such damage was done that the collection in the Hunterian Museum was reduced from 14,000 to 3800 specimens.

The characteristic feature of the wounds in World War II has been their multiplicity—to an even greater extent than in World War I. Blast wounds have been common, and small fragments of glass or other debris often enter the superficial tissues. The best form of treatment in such cases is to paint the wounds with 1 per cent gentian violet or some other weak antiseptic and allow the foreign bodies to extrude themselves. This usually takes place without complication on about the tenth day.

The great paucity of gas gangrene as compared with 1914-1918 may be attributable either to the use of the sulfonamide group of drugs or to the plaster method of treating compound fractures. The incidence has been less than 1 per cent. The wounds were undoubtedly as well cleaned and débrided in the last war, and gas-bacillus antiserum is being employed only in wounds that involve regions known to predispose to gas infection, such as the buttocks, perineum, calves and inner thighs. This type of infection is certainly not unknown in the Navy, as was formerly taught, but is much less common.

Whether the type of injury is responsible is not certain, but secondary hemorrhage—the bugbear of the base hospital during the last war—is almost unknown. Similarly, traumatic aneurysm has become much rarer.

In wounds of the face and jaws, wide excision of tissue is almost never necessary, for the blood supply is

excellent and gas gangrene is very rare. Immediate surgery is carried out if possible. Dependent drainage in fractures of the jaw is probably the most important single procedure. Whenever possible, the mucous membrane should be sutured immediately.

In the management of burns, there has been a recent trend away from the use of tannic and other eschars, especially on the face and hands, where early motion is a desirable factor. There seems to be little question that an eschar of some sort is necessary to save lives in widespread burns, but there is no unanimity of opinion regarding the face and hands. There are advocates for wet saline dressings, *tulle gras* and certain ointments.

The most frequent injuries sustained in the naval forces are those associated with mine explosions, which usually involve small commercial vessels or mine sweepers. The force is borne in the long axis of the body. Fractures of the os calcis and, to a less extent, the astragalus are most frequently seen. As might be expected, there is a high incidence of fracture of the lumbar spine in these casualties. Also encountered are fractures around the knee of the femur and of the tibia, particularly the so-called "bumper" type.

Injuries to the chest are of the same severity and frequency as those during the last war, but the treatment differs in that the wounds are usually drained for the first two or three days instead of being closed tight and subsequently aspirated. Together with abdominal wounds they are the most infrequently seen, at least in the hospitals, possibly because such a large percentage of these patients die almost immediately. The same general rule holds in naval surgery, namely, that men hit in the trunk invariably die. In abdominal wounds a complete examination is especially necessary, for there is often a very small wound of entry causing considerable internal damage. Wounds of the buttock are particularly prone to involve the peritoneal cavity, and one should always treat them with that possibility in mind. In general if wounds of entrance and exit are found in both rectus muscles, one can be fairly certain that the peritoneal cavity has not been involved. Among patients with peritoneal involvement, the mortality was highest among those under twelve years of age, but the general mortality was also high. However, cases were cited in which patients with profound wounds were saved by the use of prodigious amounts of blood and plasma, and the lesson to be learned is the necessity for large amounts of these lifesaving substances. Abdominal wounds in pregnant women have been almost universally fatal. On the other hand, few cases have been lost in maternity hospitals, even when such hospitals have been demolished, for it is usually possible to evacuate the patients in time. The prolapse of bowel in wounds of the abdomen apparently makes the prognosis much worse. Although one receives the impression that a large percentage of injuries to the bowel are fatal, statistics actually reveal a gross salvage of 40 to 50 per cent. The mortality in prolapse is about 80 per cent. Multiple wounds elsewhere in such patients are far greater in the present war, and the great lifesaving value of the resuscitation officers, with their plasma and blood makes many seemingly moribund patients operable. Abdominothoracic wounds contribute from 10 to 12 per cent of all wounds, as in the last conflict, with essentially the same recovery rate of 66 per cent. Injury to the right side offers a better prognosis for only the liver is involved, contrasted with stomach, spleen and bowel on the left side. The respective mortalities are 50 and 70 per cent.

Blunt injuries more frequently involve the thoracic than the abdominal viscera. This is also borne out by experimental work. Pathologically, multiple small subserous and submucous hemorrhages and tears are found. In naval warfare, this type of injury is sustained by survivors of sunken ships who are swimming in the water as depth charges explode.

## EVANS MEMORIAL HOSPITAL

At a meeting at the Evans Memorial Hospital on November 21, Dr. Alvah H. Gordon, emeritus professor of medicine at McGill University, Montreal, spoke on Bone Changes in Certain Medical Diseases. He emphasized the fact that bone has now become a recognized tissue with an active metabolism rather than merely a static structure with morphology. The discussion consisted of a lantern slide demonstration of certain bone changes, common and rare, seen during a long experience.

Examples were shown of typical cases of certain metabolic diseases, such as gout, rickets, scurvy and lead poisoning. The fuzzy epiphyseal line in rickets was contrasted with the sharpness of that in scurvy, and the two were differentiated from congenital syphilis, which so often occurs in the same age group. Also briefly discussed were the changes of hyperparathyroidism.

The next group concerned hormonal imbalances. In the hyperpituitarism of Simmonds's disease, a characteristic widening of the sella turcica offers presumptive evidence of the diagnosis. A case of renal rickets, which was diagnosed at autopsy and was seen by many authorities during life, was considered a case of hypopituitarism. The relatively new concept that a postmenopausal osteoporosis is caused by lack of estrogens rather than by an inadequate diet has resulted from the work of Albright. Paget's disease, characterized by both an increase of growth and a degeneration of bone, is often found more or less accidentally or as the result of a pathologic fracture. The latter are usually transverse. Multiple myeloma can usually be found in several bones and clinically is on the borderline of malignancy. The unusual character of the bone metastases in carcinoma of the prostate and breast, which are oftener productive than destructive, was pointed out. Leukemia and leukemoid states frequently reveal bone changes, and these may also be osteosclerotic in leukemic leukemia. There is an enlarged spleen, frequent backache and an elevation of the myelocyte count to high levels. An unusual case was cited in which such a process practically displaced all the active bone marrow, the spleen was enormously hypertrophied in an attempt to compensate for this displacement. Hand-Schüller-Christian's disease was mentioned in passing.

Finally, Dr. Gordon discussed achondroplasia, in which the short body is surpassed by even shorter arms. The mentality is rather good and is a definite point of differentiation of cretins and achondroplastics. Such people are invariably strong for their size. They should be classed as clever rather than intelligent, however.

## BOOK REVIEWS

*Arthritis and Allied Conditions*. By Bernard I. Comroe, M.D. Second edition, thoroughly revised. 8", cloth, 878 pp., with 242 illustrations. Philadelphia: Lea and Febiger, 1941. \$9.00.

In the second edition of this book, a number of additions have been made to keep pace with the ever-expanding

knowledge of this group of diseases. A number of faults in the first edition have been corrected. The text is more carefully written, and the descriptions are clearer. There is logical arrangement of the material. The illustrations are excellent. Unfortunately, most of them have been borrowed from publications by other men. It would add to the value of the book if there were more sketches or photographs of necessary apparatus and braces, since many of these illustrations give no clear idea of the form of the apparatus or how it should be fitted. The book is complete, as full a presentation of knowledge as is possible. In the opinion of the reviewer, the weakest chapters are those dealing with related orthopedic lesions, in which the author's experience is necessarily limited; these could be omitted without lessening the value of the book. A well-selected bibliography follows each chapter.

Although this is an excellent discussion of arthritis, probably the best yet to appear in the English language, the average reader will be dismayed by its voluminousness. In an attempt to cover completely all diseases in which there is disability in the joints, the size of the book has become rather too large to attract a busy general practitioner. Those interested in treatment of chronic arthritis will find here an up-to-date summary of physiologic, pathologic and therapeutic data. Controversial subjects are presented without bias. But the author, mature in experience, has not hesitated to state his own opinion about them. This book should be welcomed by the physician who has the time and patience to read so large a volume, and it should be particularly helpful to those who treat chronic arthritis.

---

*Stethoscopic Heart Records: Sounds, murmurs and arrhythmias.* By George D. Geckeler, M.D. Columbia Records, Set M-600. Seven records. Price \$12.75.

The faithful reproduction of heart sounds and murmurs by means of phonographic records is a feat that has tantalized and baffled sound engineers for nearly twenty years. The problems involved are extremely complex, and although this collection indicates that progress is being made, it also shows that there is still room for improvement. The technic of heart-sound reproduction involves the screening out of certain frequencies, to exaggerate other sounds that it is desired to bring out. The accomplishment of such selective exaggeration without undesirable distortion has seldom been achieved. In Dr. Geckeler's series, a good reproduction has been accomplished in about half the recordings. The most unsatisfactory are the attempts to reproduce gallop rhythm and faint mid-diastolic murmurs. The common arrhythmias, the aortic systolic and diastolic murmurs and the louder mitral diastolic murmurs are well illustrated. The best recordings are so very good that one can only hope that Dr. Geckeler will eventually succeed in bringing them all up to the same high standard. As they are, they should prove helpful in teaching auscultation to beginners.

---

*Development Diagnosis: Normal and abnormal child development; clinical methods and practical applications.* By Arnold Gesell, M.D., and Catherine S. Amatruda, M.D. 8°, cloth, 447 pp., with 20 illustrations. New York: Paul B. Hoeber, Incorporated, 1941. \$6.50.

This is an elaborate experimental research on the development of behavior in infants from the time of birth up to the second year of life. The first part of the volume

details what a child should be able to do, if it is both mentally and physically normal, at the age of four, sixteen, twenty-eight and forty weeks and twelve, eighteen, twenty-four and thirty-six months. The methods of examination are given in great detail, with proper illustrations. This part of the book should be of value to all pediatricians in quickly estimating the capacity of a child.

The second part deals with various abnormal states: amentia, endocrine disorders, convulsive and other neurologic states, cerebral injury, prematurity, precocity and environmental retardation. This section of the work is not so elaborate as the first section, but is valuable in a general way. Other clinics, with larger experience, could use the material here presented as a basis for more extensive investigations. The most important chapter, on the clinical aspects of child adoption, is full of sound advice regarding this subject from the authors, who have had extensive experience.

A further section of the book deals with diagnosis, guidance and development supervision.

In general, this work is a fundamental text from a clinic of worldwide reputation. No other recommendation is needed.

---

*Brucellosis (Undulant Fever), Clinical and Subclinical.* By Harold J. Harris, M.D. Foreword by Walter M. Simpson, M.D. 8°, cloth, 286 pp., with 12 colored and 44 black-and-white illustrations. New York: Paul B. Hoeber, Incorporated, 1941. \$5.50.

This monograph covers the history of brucellosis, as well as its etiology, epidemiology, pathology, symptomatology, diagnosis, prognosis, treatment and prophylaxis. Dr. Harris has had an active practice of medicine in a rural area and has based much of his work on the personal observations made on 250 patients with the disease. It is his opinion that infection with the disease is far greater than has generally been supposed, and that the chronic form constitutes 90 to 95 per cent of all brucellar infections. He states that this disease ranks with tuberculosis, syphilis and pneumonia in incidence, although not in mortality. He compares the disease to syphilis, because of its protean manifestations.

The major part of the book is devoted to symptomatology and diagnosis. There are colored illustrations of skin lesions and positive skin tests. Of particular interest to the practitioner is the composite picture of the most usual complaints encountered in the disease. Although farmers, dairymen and slaughterhouse workers contract the disease by direct contact, the greater part of the incidence is due to raw dairy products. The summer tourist may easily pick up the infection even though the greater part of his year is spent in areas where pasteurization is prevalent. Dr. Harris advocates the pasteurization of all milk and the destruction of all infected cattle, sheep, goats, pigs, horses and other domestic animals known to harbor the disease. Such a destruction would require a large expenditure of money, since it is estimated from surveys that between 11 and 20 per cent of all the cows in the United States are infected, and 20 per cent of the hogs in Iowa. Complete pasteurization seems possible, but at the present time, some communities and even entire states are so blind to the menace of raw milk that pasteurization is neglected.

This volume should be of great help to practitioners in communities where raw milk is consumed, and it would be a valuable addition to any physician's library.

(Notices on page xi)

# The New England Journal of Medicine

Copyright, 1942, by the Massachusetts Medical Society

VOLUME 226

MARCH 26, 1942

NUMBER 13

## PRESENTATION OF THE HENRY JACOB BIGELOW MEDAL

### INTRODUCTORY REMARKS\*

IRVING J. WALKER, M.D.

BOSTON

THE occasion of this joint meeting of the Boston Surgical Society and the American College of Surgeons is for the presentation of the Henry Jacob Bigelow Medal to one chosen by the Boston Surgical Society for outstanding contribution to the advance of surgery.

As president of the Boston Surgical Society, it seems fitting that I should remind you of something of the life of Henry Jacob Bigelow, in whose honor the award is made, as well as of the history of the Bigelow Medal.

Dr. Bigelow was born in Boston in 1818, the son of a physician who was a professor in the Harvard Medical School. His preliminary education was received in Boston schools. He graduated from Harvard College in 1837, and from the Harvard Medical School in 1841. In 1846, he was appointed surgeon to the Massachusetts General Hospital, in which capacity he functioned for the next forty years. From 1849 to 1882, he was professor of surgery at Harvard Medical School. Harvard University awarded him the honorary degree of LL.D. in 1882. He died in 1890, at the age of seventy-two.

\*This and the two following articles comprise the addresses made at the presentation of the Henry Jacob Bigelow Medal at a combined meeting of the Boston Surgical Society and the American College of Surgeons at Boston, November 7, 1941.

Much has been written of the life of Henry Jacob Bigelow. One might summarize by stating that he was a most dynamic personality of the inventive and investigative type of mind, and a clear and practical instructor of students. One of his contemporaries said, "To see him operate is to recognize a master." Dr. Bigelow contributed much to the advance of surgery.

In 1915, his son, Dr. William Sturgis Bigelow, in memory of his father, gave to the Boston Surgical Society a sum of money, the income of which was to be used from time to time for the presentation of a gold medal, to be called the Henry Jacob Bigelow Medal, for new and valuable work in surgery or connected with surgery. That the Boston Surgical Society has guarded this trust is evidenced by the names of the following internationally recognized surgeons who have received the award: William J. Mayo, William W. Keen, Rudolph Matas, Chevalier Jackson, George Grey-Turner, John M. T. Finney, Harvey Cushing and Edward W. Archibald.

Tonight, we meet to honor one who needs no introduction to the medical profession, a modest and respected gentleman, a profound student of surgical problems, an inspiring and stimulating teacher, an accomplished surgeon. I have the honor of presenting to you Dr. Allen Oldfather Whipple.

## PRESENTATION OF THE MEDAL

DAVID CHEEVER, M.D.

BOSTON

DR. WHIPPLE, having voted to confer on you the Bigelow Medal, the Boston Surgical Society has delegated to me the honor of presenting it to you. We, the members of the society, and others of your friends here assembled, including many fellows of the American College of Surgeons who are in attendance at their annual clinical congress, need no enlightenment about the reasons for this award, but citizens in other walks of life will wish to know the grounds for the bestowal of so signal an honor—an honor paid to but eight other recipients in the twenty-six years since the medal was established. A brief citation of these grounds is therefore appropriate.

Born in Persia, where you spent the formative years of childhood and boyhood, you were nevertheless not imbued with the fatalistic and mystical philosophies of the Orient but found rather the master key to life's problems in the principles of free will and self-determination bequeathed to you from seven generations of your New England ancestors. At Princeton, you received your cultural and basic scientific education, and it is an interesting example of the shrewd intuition of youth that your classmates voted you the man most likely to succeed in afterlife. Your medical degree was won from the College of Physicians and Surgeons of Columbia University, and there followed internships at the Roosevelt Hospital and the Sloane Maternity Hospital. You then entered the service of the Presbyterian Hospital as surgeon and pathologist, passing rapidly up the steps of surgical preferment until, in 1921, but thirteen years after graduation in medicine, you were appointed professor of surgery in your alma mater and director of the Surgical Service of the Presbyterian Hospital. Your post bears the name of the illustrious Valentine Mott, who, a century ago, was your predecessor as professor of surgery and as the leading surgeon in the greatest city of America.

The qualities you have displayed in this high post and the things you have accomplished must be touched on, although at the certain risk of offending your modest self-appraisal. As a surgeon, you have ever advanced the science and perfected the art; nothing in the whole field has

been alien to your interest, and to whatever special problem you have addressed yourself you have brought clarification. Whatever tissue or organ is to be the object of your beneficent attention, your procedures are based on thorough knowledge of its anatomy, its physiology and its pathology. The diseases of the upper abdomen have constituted one of your special interests. You have demonstrated convincingly the possibility of the successful extirpation of the duodenum and head of the pancreas for carcinoma; your success in the diagnosis and removal of pancreatic tumors for the cure of that distressing and fatal malady, hyperinsulism, makes you the foremost authority in that field; on the physiology and pathology of the spleen,—described by Galen as an "organ full of mystery,"—you have thrown light that has helped to establish a rational approach to surgical therapeutics. Indeed, your most recent research has, by ingenious methods, perhaps definitively settled the old problem of the nature of the circulation in the spleen and portal bed. Your common sense has told you that profundity of knowledge alone on the surgeon's part will not ensure a successful operation, that the successful technical application of that knowledge to human tissues is of equal value; therefore, you have found not unworthy of intensive study the everyday problems of suture and ligature material and of wound healing.

For twenty years, you have directed the Surgical Service of the Presbyterian Hospital, and the teaching of surgery in the College of Physicians and Surgeons. This has been a period of change in plant, in organization, in methods, in social outlook, when failure might have attended the administration of one who had not your courage, your gentleness, your practical idealism, your fairness and, above all, your intellectual integrity. You might have inspired the ancient aphorism: *Fortiter in re, suaviter in modo*. Doubtless, you have found your greatest satisfaction in the relief of human ills, but scarcely less has been your happiness in the education of young men—you are a crusader for better training in surgery, in both undergraduate and postgraduate years. Distinguished as a clinician, you have been led by your investigative point of view beyond the clinic

to fruitful study in the laboratory. In inspiring research, you have been a veritable catalyst—although perhaps the analogy is not a sound one, since the catalyst, in achieving its reactions, does not expend itself.

A full curriculum *vitae vestrae* should list the hundred titles from your pen under which you have shared your knowledge with your colleagues, should enumerate the societies in which you hold membership and high office, should report your honors, and should speak of your unselfish work in helping to create and support high standards of surgical work. It should mention the talents in

music, in painting, the interest in books and in history, which add to your Spartan qualities of courage and self-discipline attributes more Attic in their nature. It may only hint at tender personal relationships, which, through the years, have supported you by your hearthstone.

Among your avocations, I am told, is numismatics. Here, then, is a medal to be added to your collection, beautifully wrought in purest gold. It is indeed a jewel to be treasured, but it is our happy belief that it will chiefly signify to you an enduring token of the confidence and affection of fellow workers in the field of surgery.

## PRESENT-DAY SURGERY OF THE PANCREAS\*

ALLEN O. WHIPPLE, M.D.†

NEW YORK CITY

Much harm has been done in Medicine by the partial representations of those who, having a point to prove, have suppressed their unsuccessful experiments and brought into view none but favorable facts.

From the preface to *American Medical Botany*, by Doctor Jacob Bigelow, published in 1820.

**K**NOWLEDGE of the pancreas, its anatomy, physiology, pathology, symptomatology and therapy is of comparatively recent date. Less than a hundred years ago, this organ was spoken of as the abdominal salivary gland. The German term *Bauchspeicheldrüse* still connotes that meaning. Bernard,<sup>1</sup> in 1856, was the first sound contributor to the physiology of this organ in his experimental studies of the action of pancreatic juice in food digestion. Langerhans,<sup>2</sup> while still a medical student in Berlin, published his remarkable histologic studies of the pancreas as his inaugural dissertation in 1869. Using the transillumination method, as Lister<sup>3</sup> did in his study of inflammation, a method only recently revived so effectively by Knisely,<sup>4</sup> Langerhans described the several types of cells and tissues in the pancreas and by his own original methods of dye injections showed the acinar tissue to be separate from the islet tissue. These collections of cells, which he termed "our cells," were given scant notice until the French histologist, Laguesse,<sup>5</sup> recognized their anatomic importance and in 1896 called them *les îlots de Langerhans*, and Langerhans cells they have since been called.

The persistence of these islands, with atrophy

of the acinar tissue, after ligation of the pancreatic ducts, had led many observers to consider islet tissue as directly related to an internal secretion that controlled sugar metabolism. In 1889, a most significant year in the story of the pancreas, von Mering and Minkowski<sup>6</sup> for the first time demonstrated the exact role of the organ in carbohydrate metabolism and in diabetes mellitus by their experimental studies in pancreatectomized animals.

Several investigators, during the next thirty years, were on the very verge of isolating the internal secretion of islet tissue, and in more than one case made an extract to be injected into pancreatectomized animals with diabetes, but because of impurities or insufficient amounts did not accomplish the crucial result. It remained for Banting and Best<sup>7</sup> to demonstrate to a waiting world, by positive and conclusive experimental physiology, this internal secretion, since named insulin, and to apply it therapeutically in the treatment of diabetes. Their announcement of this epoch-making discovery was published in 1922.

A rapidly developing knowledge of blood chemistry as the chief aid in the study of metabolic disease was of the greatest help in the immediate acceptance of insulin therapy. But it soon became evident that overdosage caused a sharp drop in blood sugar, giving rise to the protean manifestations of so-called "insulin shock," and the avoidance and treatment of this syndrome became a major problem. During this period of four or five years after the discovery of insulin and its therapeutic complication, the idea occurred to Harris,<sup>8</sup> of Birmingham, Alabama, that overactive islet tissue, either as hyperplastic islands or as tumors of islet tissue, might account for the clinical

\*From the Department of Surgery, Columbia University College of Physicians and Surgeons.

†Valentine Mott Professor of Surgery, Columbia University College of Physicians and Surgeons, director, Surgical Service, Presbyterian Hospital.

picture of central-nervous-system disturbances associated with hypoglycemia. He discussed this possibility with Banting, who agreed with him in his hypothesis. Several years later, a physician, suffering with the syndrome of severe insulin shock in the fasting state, went to Rochester, Minnesota, and after consultation with Wilder<sup>9</sup> and William J. Mayo, the patient was operated on by Dr. Mayo, who found a tumor of the pancreas with metastases to the liver. The tissue removed at operation proved to be an islet-cell tumor. Several weeks later, autopsy corroborated the diagnosis, and biologic assay of the liver metastases showed large amounts of insulin in the tumor tissue.

In 1929, Graham,<sup>10</sup> of Toronto, removed a benign adenoma of islet tissue from a patient who was immediately relieved of her symptoms of hyperinsulinism, and has remained cured to date. This initiated a new and the latest phase of endocrine surgery, a type of surgery requiring the skill in diagnosis and operative technic previously demonstrated in the removal of tumors or hyperplasias of the thyroid, pituitary, adrenal and parathyroid glands.

The relation of islet tissue to hypoglycemic states had been noted in 1926, when Gray and Feemster<sup>11</sup> reported the finding of hyperplasia of islet tissue in an infant who was born of a diabetic mother and died in convulsions shortly after birth. The fetus had been supplying the diabetic mother with insulin, and with the sudden cessation of the physiologic demand at birth, the hyperplastic islands caused low blood sugar and insulin shock in the infant.

Clinical tests of the external secreting function of the pancreas, although still in the experimental phase and not as yet completely satisfactory, are contributing materially to the diagnosis of the acute and chronic lesions of this organ. These newer methods have replaced the older tests of the stools for pancreatic digestion. These may be divided into those useful in the differential diagnosis of the acute lesions and those in the chronic inflammatory and obstructive lesions.

Tests for the acute lesions consist of lipase and amylase determinations in the blood serum. During the early stages and for the first three or four days after the onset of acute pancreatitis, the edema of the gland shuts off the ducts, and both the obstructed lipase and amylase pass into the blood stream, giving high levels of these proenzymes in the blood. It must be emphasized that this concentration of lipase and amylase for diagnostic purposes takes place only in the first four or five days after the onset of the acute lesions. These determinations, moreover, do not differentiate the type of acute pancreatitis or the severity of the

process. Observations of these elevated serum lipase and amylase levels have been made in a number of clinics. Comfort and Osterberg,<sup>12</sup> of the Mayo Clinic, reported a series of acute pancreatic lesions, proved by the surgeon or pathologist, as follows: elevated values for serum lipase were obtained in 31 of 32 cases, and elevated values in serum amylase in 7 out of 10 cases. At the Presbyterian Hospital, using serum amylase readings, we have found elevations of 50 to 300 per cent in 44 of 60 cases. Of the 14 cases that did not show an elevation, 5 had a history of onset of the acute symptoms ten days to five weeks before the test was made, so that one may say that serum amylase determinations were significant in 80 per cent of 55 patients. We use the rather simple Myers<sup>13</sup> starch-digestion test because it is easily done, gives the result within an hour, and can be made in any laboratory by a well-trained technician, resident or intern.

The tests for determining the chronic inflammatory lesions and the chronic obstructive lesions of the pancreas are based on the work of Swedish investigators. Starling,<sup>14</sup> in 1907, reported the discovery of secretin in the succus entericus. But it was not until 1937 that Agren and Hammersten<sup>15</sup> isolated the hormone, secretin, in crystalline form. Injected intravenously, this hormone causes a great increase in the flow of pancreatic juice. Lagerlöf,<sup>16</sup> using the two-tube intubation technic, with one tube in the stomach and the other in the duodenum, was able to aspirate pure pancreatic juice in large amounts by injecting secretin intravenously in normal controls. In chronic inflammatory or sclerosing lesions of the pancreas, the response to secretin is markedly diminished. In obstructive lesions of the papilla of Vater or of the head of the pancreas, the flow is absent and differentiates these lesions from the jaundiced patients with carcinoma of the common or hepatic ducts.

More recently, the use of Mecholyl or methylacetylcholine has further elaborated the duodenal determinations of pancreatic ferments. Secretin, which is a hormone, increases the volume and alkalinity of pancreatic juice. Mecholyl, acting through the vagus, increases the concentration of the ferment without increasing the volume and alkalinity, and is a more accurate index of the activity of the acinar tissue than of the obstruction of the flow of the pancreatic juice.

Contributions to the knowledge of the pathology of the pancreas have been made chiefly by Americans. Although autopsy findings in acute pancreatic lesions had been described by Schmackpfeffer<sup>17</sup> in 1817, Clässen<sup>18</sup> in 1842, Friedreich<sup>19</sup> in 1875 and Balser<sup>20</sup> in 1882, it remained for Fitz,<sup>21</sup> the distinguished physician and pathologist of Bos-

ton, to present the first clear-cut correlation between the acute hemorrhagic and acute suppurative lesions of the pancreas and the clinical picture; he deserves full credit for calling the attention of physicians and surgeons to the entity of acute pancreatitis. It was in 1889 that Fitz delivered his famous Middleton-Goldsmith Lecture before the New York Pathological Society.

More recently, a new chapter in the pathology of the pancreas has been added by pathologists and clinicians of this continent in their studies of islet-cell tumors. These tumors were practically unknown until their clinical significance was recognized.

In 1926, Warren,<sup>22</sup> of Boston, was able to collect only 20 cases of islet adenoma, 4 of them his own, from the entire literature. At that time, no clinical significance was attached to these growths. With the removal of the carcinomatous islet tissue in 1927 by Dr. Mayo and the islet adenoma in 1929 by Dr. Graham, interest in this remarkable endocrine tumor increased rapidly. Since then, over 100 patients have been operated on, and most of these tumors have been found by surgeons at operation; this is rather a sad commentary on the care with which the pancreas is usually sectioned and examined on the autopsy table. These adenomas are, of course, small, averaging not more than a centimeter in diameter, but they should be found more easily by the pathologist than by the surgeon. The pathology of the tumors and the difficulty of grading them have been carefully studied in our laboratory and reported by Frantz.<sup>23</sup>

This review of the contributions to knowledge of the pancreas is given because of its bearing on present-day ideas of therapy. During the past five to ten years, surgeons have become more conservative in the treatment of the inflammatory lesions and more radical in the surgery of the tumors of the pancreas, and this attitude is the result of the increasing knowledge of the physiology and pathology of this organ, the additions to the diagnostic armamentarium of clinical tests, and the means of combating jaundice and shock in operations for cancer of this gland.

#### ACUTE PANCREATITIS

This lesion as now accepted may vary from an acute edema to a complete necrosis of the entire organ. The pathogenesis of the several varieties of acute pancreatitis is still undetermined. It is definitely established that factors of trauma, vascular injury, infection and bile invasion or bile reflux can initiate and continue the process of acute inflammation. It is probable that the toxic effect of the lesions showing acute hemorrhage and acute necrosis, and evidenced by shock and collapse, may be associated with any of the above inciting

factors, and that it is probably the result of decomposition of proteins or protein-split products by bacteria or their proteolytic enzymes. The exact nature of the poison or poisons causing the shock and collapse remains speculative. The fact that in the majority of these acute lesions there is associated biliary-tract disease points to a close relation of bile invasion as the commonest factor in the pathogenesis, and favors the "common-channel" theory.

Until recently, it was generally accepted that bile or duodenal contents, as an inciting factor, activated the proenzyme, trypsinogen, converting it into trypsin, and that by its action, autodigestion of the parenchyma of the pancreas took place. This idea seemed to be borne out by the experiments of Guleke<sup>24</sup> and Pólya<sup>25</sup> in Germany, and of Sweet<sup>26</sup> in this country. It should be pointed out that the pancreatic tissues they worked with were not sterile. More recently, however, very carefully checked experiments by Dragstedt and his associates,<sup>27</sup> at the University of Chicago, have cast great doubt on the theory of autodigestion, and point convincingly to the evidence that the acute pancreatic lesions, commonly associated with bile invasion of the ducts, are the result of the destructive action of bile salts and that the bacteria in the ducts and pancreatic tissue, especially the anaerobes growing in the damaged or necrotic tissue, increase the damage and give the toxic symptoms. Dragstedt's discussion deserves the most careful attention of every student of this subject.

In the clinical picture of these severe lesions, shock is the most serious phase of the symptoms and signs. In the milder form of edema of the pancreas, shock is usually not evident, but in the hemorrhagic and necrotic varieties shock is so serious that it is the only condition that should be treated at first. It is manifested by great hemoco-concentration, low blood pressure, rapid pulse and vasomotor atony. It should be treated by plasma transfusion, physiologic saline solution and adrenocortical extract. If surgery is resorted to before the shock is relieved, the mortality will be as high as it has always been—around 50 per cent.

Inasmuch as the same symptom picture is seen in other acute upper abdominal lesions,—especially in high-strangulation ileus and perforated ulcer, in which operative delay is so hazardous,—the differential diagnosis of acute pancreatitis is most essential. It is in these conditions that serum amylase and lipase readings are of the greatest help, as are three-position films of the abdomen to determine fluid levels in the small intestine in ileus and in subphrenic and subhepatic areas in perforation of the gastrointestinal tract. If serum amylase readings are definitely elevated and fluid



levels and free air are ruled out by x-ray examination, the diagnosis of acute pancreatitis can be safely made, the patient can be treated for shock, and surgery can be delayed. Many of these patients, the majority in fact, show such marked improvement in six to twelve hours that surgery can be postponed for associated biliary lesions or for localizing pancreatic inflammation or abscess formation. There is no doubt that this conservative policy, now followed in a number of surgical clinics in various parts of the country, has lowered the mortality of acute pancreatitis. In our experience in the past five years, the mortality has been 15 per cent in 46 cases of acute pancreatitis of various grades, as proved by delayed operation or by autopsy. In the two previous five-year periods, when operation was done as soon as the diagnosis was made, the mortality had been 35 per cent.

We prefer the serum lipase to the amylase test. We use the Myers<sup>13</sup> test, which employs the serum in graded dilutions of starch, to determine the amylase action.\* This test can be done within an hour and by any of the laboratory technicians, residents or interns trained in its use.

#### CHRONIC PANCREATITIS

The surgery in these lesions, vague and uncertain as they are to diagnose clinically, has not made any definite advances. In the cases associated with jaundice, short-circuiting operations, like cholecystoduodenostomy and cholecystojejunostomy, but preferably choledochoduodenostomy, are indicated for two reasons: to relieve the intolerable itching, and to improve fat digestion. Diagnostic tests of pancreatic secretion, using a duodenal tube and secretin and Mecholyl intravenously, are of value in differentiating chronic pancreatitis and cancer of the pancreatic head with complete duct obstruction.

#### CYSTS OF PANCREAS

The differential diagnosis of pancreatic cysts will always be a fascinating problem in abdominal masses. A recent history of upper abdominal crisis

\**Method:* To one tube (A), add 2 cc. blood (or serum), 7 cc. water and 1 cc. 1 per cent starch solution (freshly boiled and cooled); to another tube (B), add 2 cc. blood (or serum) and 7 cc. water. Mix and incubate both tubes exactly fifteen minutes at 40°C. Chill promptly in ice water, and add about 0.5 gm. picric acid to each tube and 1 cc. of the starch solution to B; filter. To three Folin sugar tubes graduated at 25 cc., add: 3 cc. filtrate from A; 3 cc. filtrate from B; and 3 cc. standard .02 per cent glucose solution saturated with picric acid. To each tube, add 1 cc. 20 per cent sodium carbonate solution; mix; place in boiling water for fifteen minutes; cool; dilute to 25 cc.; and mix. Compare the A and B mixtures with the glucose standard in a colorimeter. The amount of glucose in each is calculated according to the following formula:

$$\frac{\text{Standard reading}}{\text{Unknown reading}} \times 0.06 \times \frac{1}{0.6} = \text{mg. glucose per cc. blood (or serum).}$$

The difference in glucose contents of the two tubes (A and B), expressed in mg. per cc., multiplied by 20 equals the amylase value of the blood (or serum) in Myers and Killian units. One unit of amylase equals milligrams of glucose formed by 20 cc. of blood and 100 mg. of starch in fifteen minutes under experimental conditions. If the value in any sample is higher than 40 units, the test should be repeated, using 1 cc. (or 0.5 cc.) of blood (or serum).

or trauma should always make one think of pancreatic pseudocyst in the presence of a mass in the upper abdomen, especially one to the left of the midline. These so-called "pseudocysts" following trauma or acute pancreatitis develop, as a rule, more rapidly than the retention cysts, the cystadenomatous cysts and the so-called "dermoid cysts" in the pancreatic area. The pseudocysts are unilocular, are usually not lined by epithelium, and when marsupialized or drained are not followed by persistent fistula, as a rule, and therefore give better late results. In the diagnosis of any large pancreatic cyst, a simultaneous barium meal and a barium enema for x-ray studies are of great help in differentiating the lesion from splenomegaly, renal tumor, mesenteric cyst and retroperitoneal masses. A pancreatic cyst pointing forward through the gastrohepatic omentum will push the stomach downward; one pointing through the gastrocolic omentum will push the stomach upward and the colon downward; and one pointing through the mesocolon pushes the colon upward.

Only a small percentage of pancreatic cysts can be completely removed, because of their deep position, their relation to vital structures and their frequent association with large, friable, vascular channels. For this reason, when one explores the abdomen and finds such a cyst, it is imperative to determine by careful inspection, before any attempt is made to excise it, the question of whether or not the cyst is removable; for once the attempt is begun, if it has to be abandoned because of hemorrhage or damage to such vessels as the midcolic, the superior or inferior mesenteric or the portal vein, the mortality rate rises to a high level.

If the cyst is found to be cystadenomatous, multilocular and involving the major portion of the pancreas, it had best be left alone, since marsupialization or drainage will result in a distressing pancreatic fistula. Cystadenomatous cysts in the tail of the pancreas can be removed successfully, but not those in the head and body.

In the unilocular cysts that cannot be excised, marsupialization or drainage should be used. To avoid the skin irritation and the uncomfortable wet dressings from fistulous fluid, continuous suction should be applied through a catheter inside a larger rubber tube placed in the cyst during the postoperative period while the cyst cavity is contracting. After a few days, with decrease of fistulous flow, sclerosing solutions such as those used in the injection treatment of varicose veins frequently diminish the flow of pancreatic juice and within three to four weeks stop it entirely. In

cases in which the fistulous tract persists, it is possible to transplant the tract into the stomach or jejunum. We have marsupialized two large dermoid cysts arising from the region of the body of the pancreas, and at a second operation, in one patient, we were able to excise the remaining fistulous tract, with permanent cure.

### TUMORS OF PANCREAS

A discussion of the surgery of the tumors of the pancreas is a complex subject, surgically simple and agreed to when the growths are benign, but complicated and controversial when they are malignant. Before the discovery of insulin in 1922, which clarified the question of the internal secretion of the pancreas, only a small number of successful removals of benign tumors had been reported. In 1924, Gross and Guleke,<sup>28</sup> in their comprehensive monograph on the diseases of the pancreas, in the section on the treatment of tumors of the pancreas, were able to find only 6 cases of benign tumors removed by operation and reported in the literature. With the report by Wilder and his associates<sup>9</sup> in 1927 of the carcinoma of islet tissue operated on by Dr. Mayo and the paper of Howland et al.<sup>10</sup> describing the first successful removal of an islet-cell adenoma by Dr. Graham in 1929, a new field of endocrine surgery was opened, and since then, in a period of twelve years, over 100 islet-cell tumors have

### Islet-Cell Tumors

The majority of islet cell tumors are microscopically benign adenomas, but a certain number are questionably malignant because of capsule invasion or the finding of islet cells in the blood vessels of the tumors. A minority of such tumors

TABLE 2 *Résumé of Cases Operated on at the Presbyterian Hospital to November 1, 1941, for the Removal of Islet Cell Tumors*

	No. of Cases
Patients operated on	22*
Tumor found at first operation	19
Tumor found at second operation	3
Benign adenomas removed	21
Questionably malignant tumor removed	1
More than one tumor found	2
Operative deaths	2 (9%)
Due to pneumonia	1
Due to thyroid storm	1
Subsequent death (malignant tumor)	1

\*In 16 of the 19 survivors operation resulted in cure

are obviously malignant, as shown by metastases to the liver or adjacent lymph nodes. A review of the literature and personal communications from surgeons who have kindly sent me reports of their operated cases, as well as our own cases, are referred to in Tables 1 and 2.

It is impossible in this lecture to go into the details of the pathology, symptomatology and treatment of these tumors,<sup>29</sup> but certain points should be emphasized.

Disorders of the liver, adrenal, pituitary and thyroid glands, and thalamus, in which hypoglycemia occurs, must be ruled out.

The syndrome associated with islet-cell tumors must present the following essential triad: attacks of central-nervous-system disorder—motor, vasomotor or psychic—coming on during the fasting state; fasting blood-sugar levels of 50 mg. per 100 cc. or less; and immediate recovery from these attacks on the administration of glucose by mouth or by vein. Unless this triad is present, the diagnosis of a tumor requiring surgery should not be made. In a review of 105 cases of islet-cell tumor removed by operation, only one patient showed a fasting blood sugar above 50 mg. per 100 cc., and his reading was 53 mg. Because we have adhered to this rule, we have found islet-cell tumors at the first operation in 19 of 22 patients, whereas in another clinic, in which the rigid criteria were not followed, tumors were found in only 16 of 46 cases.

In the majority of epileptic and narcoleptic patients with disturbed blood sugar levels, the triad is not found, but in the doubtful cases, electroencephalograms now give tracings charac-

TABLE 1 *Résumé of Hypoglycemia Cases\* to November 1, 1941.*

	No. of Cases
Operation	158
Tumor found	105
No tumor found	53
No operation tumor found at autopsy	29
Cases in which tumor found	134
Benign adenomas	101
Questionably malignant tumors	22
Carcinoma with metastases	8
Harrmaroma	1
Undifferentiated tumors	2
Tumor overlooked at operation	10
Found at second operation	6
Found at autopsy	4
Multiple tumors	9
Found at operation	7
Found at autopsy	2
Postoperative deaths (105 patients)	16 (15%)
Deaths after leaving hospital	81

\*Cases reported in the literature or by personal communication  
 †Of these, 6 patients had carcinoma with metastases

been removed. The pathology, the typical syndrome, the diagnosis and the indications for surgery and the technic of the operation in this group of lesions have now become clarified and standardized, and the results, in qualified hands, are amazingly good

teristic of epilepsy and help to establish the differential diagnosis.

In patients with the definite triad in whom serious hepatic, pituitary, adrenal and thyroid disease has been ruled out, surgery is definitely indicated and should not be delayed, for the following reasons: the continued enormous daily intake of carbohydrate required to prevent hyperinsulin shock results in rapid and marked obesity and makes these patients bad operative risks, and the surgical procedures exceedingly difficult; the repeated attacks of insulin shock or prolonged hypoglycemic states favor subsequent mental instability and deterioration; and the tumors, if questionably malignant while still localized, may metastasize and become inoperable.

In an exploration for these tumors, a thorough search of the mobilized tail, body and head of the pancreas by inspection and palpation must be made, to reveal the tumor or tumors, for more than one may be present. To palpate the head of the pancreas the duodenum must be mobilized to the left, exposing the posterior surface of the head. We have found more than one tumor in 3 cases, and we have removed a tumor from the posterior aspect of the head in 4 patients who had previously been unsuccessfully explored. Five other such secondary operations have been reported, and in 3 autopsies, tumors overlooked at operation have been found.

After such a thorough search has been made and no tumor found, the question of subtotal pancreatectomy must be decided.

Regarding pancreatectomy, mere removal of the tail or less than half the pancreas will not cure the patient. David,<sup>30</sup> of Chicago, has very recently reviewed the indications and results of subtotal pancreatectomy for hypoglycemia. In 22 patients on whom a partial or subtotal resection of the pancreas was done for hypoglycemic attacks, a tumor was found at operation in 18 cases and at a second operation in 4. There were 5 post-operative deaths; 16 of the 17 survivors were cured. It might be said that the tumor should have been discovered at the first operation in all these 22 cases if the organ had been properly immobilized and palpated.

Thirty-five patients, in whom no tumor was found in the excised pancreatic tissue, underwent subtotal pancreatectomy. David divides these cases into two groups. The first group included those in which a partial resection, less than half the organ, was done (18 cases); of these, 15 showed normal pancreas and 3 hyperplasia of islet tissue. Four patients died. Of the 14 survivors, 3 were symptom free, 3 moderately improved, and 8 unimproved. In the second group (17 patients), 35

to 60 gm. of the pancreas was removed, at least two thirds of the organ; of these, 14 showed normal pancreas, 2 hyperplasia, and 1 pancreatitis. One patient succumbed. Of the 16 survivors, 11 were symptom free (7 of these were followed for over two years), 1 was improved, and 4 were unimproved (2 of these had fasting blood-sugar values of 65 to 70 mg. per 100 cc. before operation).

Thus, it is evident that the patients with excised tumors gave far better results than the partially pancreatectomized cases and that the patients in whom no tumor was found gave about 60 per cent cures if 40 to 60 gm. of pancreatic tissue was removed.

In the study of these islet-cell tumors, certain incongruities are notable. The size of the tumor has no relation to the severity of symptoms. The largest tumor in our series gave no symptoms of hyperinsulinism and did not suggest the islet-tumor syndrome. Brunschwig's<sup>31</sup> patient, who had the largest tumor on record (15 by 13 by 10 cm.), did not have lower fasting blood-sugar values or more severe symptoms than many of those with tumors 1 or 2 cm. in diameter. A patient may have a severe convulsion one day, with a fasting blood-sugar level of 45 mg. per 100 cc., and only slight confusion or disorientation the next day, with a reading of 30 or 25 mg. per 100 cc.

The blood-sugar level after a fast of twelve to fifteen hours is a far more reliable test of islet-cell function than the glucose-tolerance curve. We have come to consider the latter entirely unreliable as a differential test, and regard it as a liver-function rather than a pancreatic-function test.

The role of the other organs of internal secretion in the hypoglycemic state of islet-cell tumors is not understood and offers room for much speculation. Without doubt, the pituitary, adrenal and thyroid glands play a more important part than any of the other endocrine organs in exerting some contrainsular or regulating mechanism by secretions opposing the activity of islet tissue. The thyroid gland may be overactive in some of these cases of islet tumor, and with the removal of the tumor, a fatal thyroid storm or crisis may occur. We have had 1 death—1 of the 2 deaths in our cases of benign adenoma—from this cause, and 3 similar cases have been reported.

In every suspected islet-tumor case, the basal metabolic rate should be determined, and if it is at all elevated,—that is, with any reading 'over +15 per cent,—operation should be delayed until the patient has been given a course of Lugol's solution, as in a case of toxic goiter.

We have made tissue cultures from 12 of the 19 tumors that we have removed. The tumor cells

grow readily as epithelial sheets—as well as the connective tissue cells of the stroma. Early in our work, the idea occurred to us of transplanting the tumor cells, which had been grown in the plasma of a diabetic patient, into the areolar tissue of the axilla or groin of this patient. We have tried such transplantations in 4 severe cases of diabetes, with the hope and rationale that the physiologic demand of the patient, on cessation or reduction of insulin, would stimulate the islet cells to grow and supply insulin. In none of the patients so treated, however, was there any evidence of growth or of decreased insulin requirement.

### *Malignant Tumors*

Unfortunately, the surgery of the malignant acinar growths of the pancreas and its closely related ampullary region, involving the common bile duct and duodenum as well as the papilla of Vater and the pancreas, is quite another problem. In cancers of this area,—because of pain and indigestion common to so many upper abdominal functional and organic disturbances and jaundice common to both liver and extrabiliary lesions,—the diagnosis is usually so long delayed that when, as a last resort, these patients are turned over to the surgeon by the diagnostically minded internist, operation reveals a cancer irremovable because of infiltration of adjacent structures or diffuse metastases to the lymph nodes and liver.

A discussion of the surgery of these malignant growths, both past and present, requires a very open mind in evaluating the cruses for the slow progress attained and the advantages and disadvantages of the methods and techniques that during the last five or six years have been developing comparatively rapidly in the radical surgery of these lesions.

The idea of a wide removal of cancers of the ampullary area and pancreatic head was first elaborately described by Desjardins<sup>32</sup> in 1907, and independently by Sauvage<sup>33</sup> in 1908. Both investigators advocated a duodenopancreatectomy. Desjardins advised a one stage operation, which included a gastroenterostomy, a cholecystenterostomy and an implantation of the pancreatic stump into the distal end of the severed duodenum. Sauvage recommended a two-stage procedure, with a gastroenterostomy in the first stage, and a duodenopancreatectomy, with exteriorization of the pancreatic stump to the skin, in the second stage. Neither one of these surgeons carried out his operation in human subjects. The magnitude of the operation in a depleted patient, as well as the bleeding tendency associated with deep jaundice, deterred all but the most ruthless surgeons from attempting such a procedure. Kausch,<sup>34</sup> in 1912, published a report of the first successful opera-

tion with duodenopancreatectomy for carcinoma of the ampulla. He performed the operation in two stages: at first, a cholecystenterostomy and ligation of the common duct and, later, with relief of jaundice, a gastroenterostomy, closing the pylorus, and, after removal of the duodenum and head of the pancreas, suturing of the lower end of the duodenum over the pancreatic stump, which preserved the flow of pancreatic juice into the intestine; the patient lived for nine months but died of an ascending cholangitis. This deep seated conviction that the flow of pancreatic juice into the intestinal tract must be maintained was one of the factors that made the mortality of the operation prohibitive for the next thirty years. Another factor, and one that explained the high incidence of hemorrhage, peritonitis and duodenal and pancreatic fistula in these procedures, whether radical or by transduodenal removal of ampullary cancers was the universal use of absorbible catgut suture and ligature material in these operations. The activated trypsinogen digested the catgut so rapidly that hemorrhage and leakage were almost inevitable. Surgeons dreaded using nonabsorbible material such as silk or linen because of the contaminated field. As a result of the hazard of the radical operation, from 1899, when Halsted<sup>35</sup> reported the first successful removal of an ampullary cancer, to 1935, the transduodenal route was, with few exceptions, the method used in the 76 cases collected from the literature and reported by Hunt and Budd<sup>6</sup> in 1935.

Following a fatal outcome, which was due to a duodenal fistula and peritonitis, in a transduodenal excision of an ampullary carcinoma that I performed in 1935, we decided to undertake a more radical operation in two stages for the following reasons: patients with ampullary cancer were able to survive for months deprived of both biliary and pancreatic drainage into the intestinal tract, and showed an atrophy of disuse of the acinar tissue of the pancreas, if bile could be restored by a short-circuiting procedure, the bleeding tendency would be corrected and digestion of fat improved; and in a later, second-stage operation, radical removal of the duodenum and head of the pancreas, wide of the growth, could be undertaken.

Dragstedt,<sup>37</sup> in 1918, was the first to demonstrate that animals could survive after a complete duodenectomy, and Mann and Kawamura,<sup>38</sup> in 1922, corroborated this observation. It was known that in some cases, as in Kausch's case, duodenopancreatectomy had been done, but without exclusion of the pancreatic juice from the intestinal tract.

In 1935, I assisted Dr. William Barclay Parsons, Jr., in operating on the first patient for whom the two stage procedure was employed.<sup>13</sup> In the second

stage of the operation, a partial duodenectomy and excision of part of the head of the pancreas, with duodenoduodenostomy but with exclusion of the pancreas from the intestinal tract, were ac-

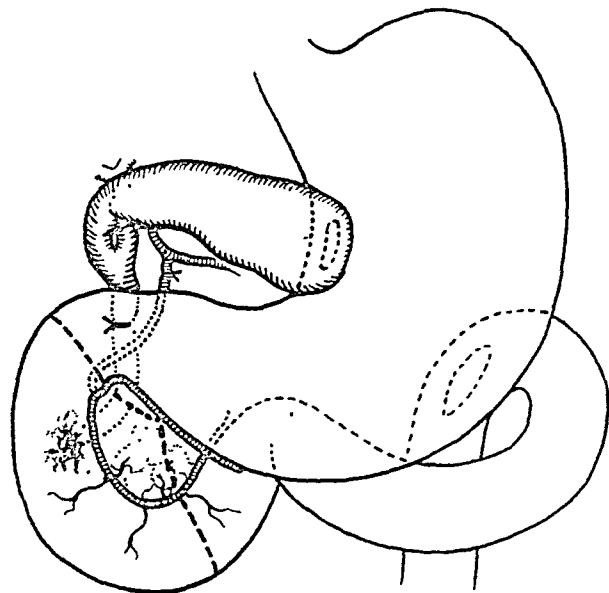
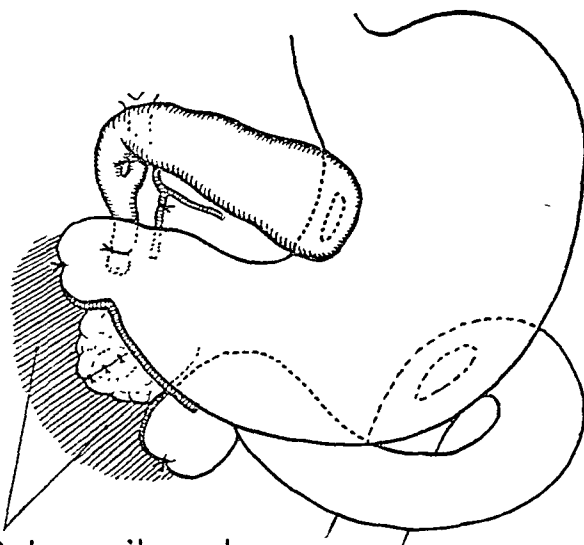


FIGURE 1. First Stage: Cholecystgastrostomy and gastroenterostomy, with ligation of the common duct.

complished. The patient developed a duodenal stenosis requiring a later gastroenterostomy. In the second case in the same year, I performed a



Retroperitoneal  
Area to be drained.

FIGURE 2. Second Stage: Ligation of the gastroduodenal artery and duodenectomy, with removal of part or all of the head of the pancreas.

total duodenectomy, with excision of part of the head of the pancreas, a cholecystgastrostomy and gastroenterostomy having been done in the first stage (Figs. 1 and 2). This patient lived twenty-

eight months, but succumbed to liver metastases. Both patients digested 80 to 85 per cent of a measured fat intake on more than one determination several months after the operation. But both developed cholangitis.

Because of the tendency for infectious material to be forced into the gall bladder by the vigorous contractions of the stomach and a tendency to stenosis of the cholecystgastrostomy opening, with biliary stasis and infection, we<sup>40</sup> modified the short

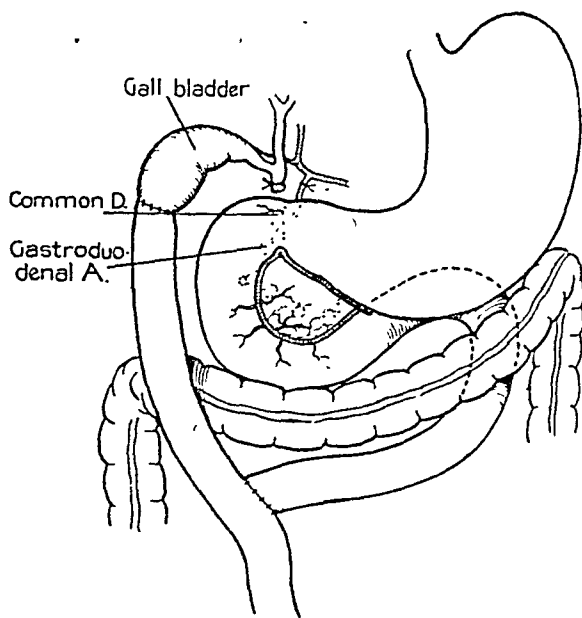


FIGURE 3. First Stage: Cholecystjejunostomy and end-to-side jejunojejunostomy, with or without a gastroenterostomy.

circuiting procedure in the first stage to an end-to-end cholecystjejunostomy with end-to-side jejunojejunostomy on the Roux principle (Figs. 3 and 4). In 34 cases, the majority of them palliative procedures, we have found a very low incidence of cholangitis and advise it rather than a cholecystgastrostomy.

Now that bleeding in jaundiced patients can be prevented with vitamin K and bile salts, liver damage can be repaired by vitamin B and a high-protein and high-carbohydrate diet, and shock can be averted by continuous spinal anesthesia and whole-blood plasma and serum transfusions, it is possible in early and selected cases to carry out these radical operations safely in one stage. This avoids the hazard of two anesthetics and two major procedures with the handicap of the adhesions following the first stage. We performed the first successful one-stage radical duodenopancreatectomy on March 6, 1940, removing the distal third of the stomach, the entire duodenum and the head of the pancreas, with an antecolic gastro-

jejunostomy and implantation of the dilated common duct into the jejunum (Fig. 5). This was

or hypoglycemia nineteen months after operation. The second patient, on whom we performed a simi-

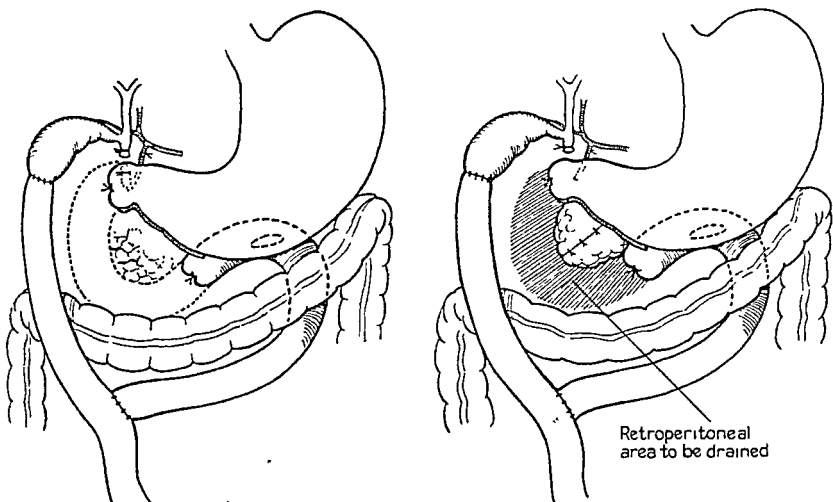


FIGURE 4. *Second Stage: Duodenectomy, with removal of part or all of the head of the pancreas. If a gastroenterostomy has not been done in the first stage, it must be done in the second stage.*

done for a carcinoma of the head of the pancreas that on section proved to be an islet-cell carcinoma without evidence of hypoglycemia. The patient, a

lar one-stage procedure in September, 1940, succumbed to a postoperative pneumonitis on the fourth day. The third operation with the one-

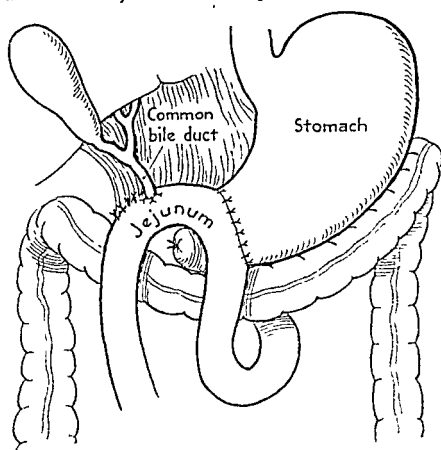
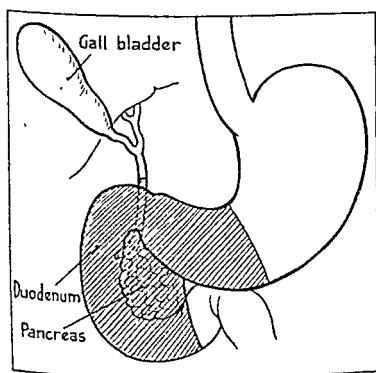


FIGURE 5. *One-Stage Radical Duodenopancreatectomy, with Antecolic Gastrojejunostomy and Implantation of the Common Duct into the Jejunum.*

forty-seven-year-old woman, had no postoperative complications, regained 20 pounds, and was free from any signs of recurrence, jaundice, cholangitis

stage procedure has been done too recently to be reported as a result.

Shortly after our first one-stage operation, Trim-

ble,<sup>41</sup> of Baltimore, independently performed a similar operation for a carcinoma of the ampulla. This patient was well and free from evidence of recurrence eighteen months after the radical operation.

But both the two-stage procedure and the one-stage procedure, as reported in the literature and in personal communications to me by surgeons who know of my interest in the subject, carry with them certain hazards and complications that must be eliminated and present problems that must be solved before these radical operations can be generally accepted. The two most serious complications are postoperative biliary and pancreatic fistulas (Table 3). In the 54 cases I have collected, the incidence of fistulas has been 10 biliary, 11 pancreatic and 2 duodenal. Duodenal and pancreatic fistulas usually close spontaneously, but biliary fistulas seldom do. The biliary fistula is due

very have been gathered from studies in dogs. It is generally agreed that in these experimental animals total pancreatectomy followed by survival with insulin therapy has resulted in fatty degeneration of the liver and alterations in blood-lipid level. Montgomery,<sup>43</sup> in his most recent work, corroborates previous studies showing that total ligation of the pancreatic ducts with complete isolation of the pancreas from any communication with the gastrointestinal tract results in the same alteration in the blood and liver lipid content and a fatty degeneration of the liver. He also corroborates the claim that administration of raw pancreas and inactivated pancreatic juice, in large amounts, will prevent these changes. Dragstedt<sup>44</sup> maintains that pancreatic juice will not prevent this disturbance in fat metabolism in pancreatectomized dogs but that raw pancreas will do so; he states that it i

TABLE 3. *Résumé of 54 Cases of Radical Pancreaticoduodenectomy Collected to November 1, 1941.*

DIAGNOSIS	TWO-STAGE OPERATIONS	POST-OPERATIVE DEATHS	ONE-STAGE OPERATIONS	POST-OPERATIVE DEATHS	FISTULAS		
					DUODENAL	BILIARY	PANCREATIC
Carcinoma of ampulla	14	2	4	2	0	5	6
Carcinoma of pancreas	21	9	5	2	2	5	4
Carcinoma of duodenum	2	1	2	1	0	0	0
Carcinoma of common duct	3	0	1	1	0	0	1
Sarcoma of duodenum	0	0	1	0	0	0	0
No carcinoma	0	0	1	0	0	0	0
Totals	40	12	14	6	2	10	11
		Total operated cases	54				
		Postoperative deaths	18				
		Operative mortality	33 per cent				

to the cutting through of the silk or linen ligature used in tying off the common duct. It is undoubtedly a better procedure, when possible, to implant the severed end of the common duct into the loop of jejunum used in the gastrojejunostomy in the one-stage operation, or into the jejunal segment leading to the jejunojejunostomy in the two-stage procedure. Pancreatic fistula can be avoided if the open end of the dilated pancreatic duct is ligated carefully with silk and the V-shaped excision in the pancreas closed or the whole stump of the cut pancreas tied with a silk ligature, as advocated by Brunschwig and Clark.<sup>42</sup>

The question whether the maintenance of the flow of the external secretion of the pancreas into the gastrointestinal tract is essential to the welfare and life of the patient has been debated, especially in the last two years. Both experimental and clinical data, reported by various observers, are in disagreement on this important subject. Some investigators maintain that the external secretion of the pancreas contains the factor that is essential for the control of fat metabolism in the liver. Others do not agree with this statement. Almost all the experimental data in this contro-

not the choline or the lecithin in the raw pancreas that produces this effect, but that the active principle is a fat-free substance, obtained in an active, alcohol-soluble extract of the pancreas. He believes that this substance is a specific hormone and has named it "lipocaic." Very recently, in discussing this entire subject of lipocaic and exclusion of the external secretion of the pancreas from the gastrointestinal tract, Dragstedt<sup>45</sup> kindly gave me his most recent views on the subject:

You will be interested to know that all scientific workers are now willing to agree with us that the beneficial effect of lipocaic cannot be accounted for on the basis of its content of choline, lecithin or the generally nonspecific lipotropic action of proteins. Confirmation of our claims in this regard has come from a number of different laboratories, including the one at Toronto.

The claim of Montgomery and his associates that lipocaic is present in the external secretion of the pancreas cannot be considered as proved by the experiments that they present. In our first paper, we demonstrated conclusively on nine depancreatized animals that the administration of fresh, active pancreatic juice in amounts up to 1000 cc. per day not only did not prevent the onset of fatty livers in these animals but

actually accelerated it. Montgomery's claim that inactivated pancreatic juice, when given by mouth, exerts a protective action is not warranted by the data that he presents, in my judgment. I expect to refer to this in considerable detail in a forthcoming publication. The effect of complete occlusion of the pancreatic ducts on the incidence of fatty infiltration of the liver in experimental animals has yielded conflicting results in the hands of different workers. In our experience, the majority of such animals do not develop the extensive degree of fatty infiltration that is seen in the depancreatized dog in the same period. I believe that the discrepancy in the results of various investigators, as well as the variations in the appearance of fatty livers in individual duct-ligated dogs, depends very largely on the extent of degeneration in the pancreas that takes place, as well as on the diet that is given to these animals. Ligation of the pancreatic ducts results in extensive destruction of the pancreas, whereas diversion of the pancreatic juice to the exterior by means of an appropriate fistula may leave the pancreas quite intact. The fact that animals with pancreatic fistula do not develop fatty livers when the pancreas remains normal indicates that fatty infiltration of the liver is not due to the absence of pancreatic juice from the intestinal tract. The presence of a moderate degree of fatty infiltration of the liver in a minority of the animals following ligation of the pancreatic ducts seems, therefore, to be due to the atrophy of the pancreas that takes place in these animals. There is evidence that this atrophy affects the islets as well as the parenchyma in some cases.

Furthermore, our<sup>46</sup> studies of the fat digestion in patients with complete duodenectomy and total exclusion of pancreatic juice from the gastrointestinal tract have shown fat digestion of 80 to 85 per cent of a carefully measured fat intake, and in a patient who came to autopsy nine months after the radical operation, fatty degeneration of the liver was not found. Schnedorf and Orr,<sup>47</sup> in a recent study of 35 cases of carcinoma of the pancreas and 17 cases of ampullary carcinoma, found only 10 cases that showed fatty degeneration at autopsy. In only 1 of our 5 patients surviving for periods of five to twenty-eight months after the radical operation have we found a disturbed fat metabolism. This patient loses 40 to 50 per cent of her measured fat intake, but is able to digest her fat by the taking of a preparation called Holadin, a pancreatic substance particularly rich in lipase.

Thus, it is evident that the question of disturbed fat metabolism in a patient whose pancreas is completely isolated from the gastrointestinal tract is not as yet completely answered, and only a large number of patients surviving the operation from three to five years will provide the necessary data for an accurate statement in this regard. It may be necessary to renew the efforts to re-establish the communication between the pancreas and the gas-

trointestinal tract in the radical removal of these ampullary and pancreatic cancers. The proposal of Kauer and Glenn<sup>48</sup> to implant the stump of the pancreas into the posterior wall of the stomach may be the answer to this problem. In the meantime, the feeding of lecithin, pancreatic extract and lipocain to patients that show abnormal blood lipid levels and deficient fat digestion before and after the radical operation is clearly indicated to maintain fat metabolism and to prevent fatty changes in the liver.

The radical operation for these tumors of the ampullary region and pancreas, based on the principle of wide, en bloc removal of the tumors, as required in modern cancer surgery, is evidently in an evolutionary stage. Many more cases, with five-year survivals, will be required before valid claims can be made for the operations as done at present. But it must be remembered that these patients untreated have an average of six months' survival from onset of symptoms until death. Many of them are tortured with the uncontrollable itching of obstructive jaundice. The considerable risk of 30 to 35 per cent is justified if they can be made comfortable even for a year or two. If only these patients could and would be referred to the surgeon before they are studied to death, while the cancer is small and localized and before the patients are seriously ill with weeks of obstructive jaundice, a far lower operative mortality and a much longer survival would result.

180 Fort Washington Avenue

## REFERENCES

1. Bernard, G. Mémoire sur le pancréas et sur le rôle du suc pancréatique dans les phénomènes digestifs. *Compt. rend. Acad. d. sc. (Supp.)* 1:379-563, 1856.
2. Langerhans, P. *Beiträge zur mikroskopischen Anatomie der Bauchspeicheldrüse*, 32 pp. Berlin: Lange, 1869.
3. Lister, J. On the early states of inflammation. *Philosoph. Transactions* 148:645-702, 1858.
4. Kniely, M. H. Microscopic observations on circulatory systems of living transilluminated mammalian spleens and parturient uteri. *Proc. Soc. Exper. Biol. & Med.* 32:212-214, 1934.
5. Laguesse, E. Recherches sur l'histogénèse du pancréas chez le mouton. *J. de l'Anat. et physiol.* 32:171-198, 1896.
6. von Mering, J., and Minkowski, O. Diabetes mellitus nach Pankreas-Exstirpation. *Arch. J. exper. Path. u. Pharmacol.* 26:371-387, 1889.
7. Banting, F. G., Best, C. H., Collip, J. B., Campbell, W. P., and Fletcher, A. A. Pancreatic extracts in the treatment of diabetes mellitus preliminary report. *Canad. M. A. J.* 12:141-146, 1922.
8. Harris, S. Hyperinsulinism and dysinsulinism. *J. A. M. A.* 83:729-733, 1924.
9. Wilder, R. M., Allen, F. N., Power, M. H., and Robertson, H. E. Carcinoma of the islands of the pancreas hyperinsulinism and hypoglycemia. *J. A. M. A.* 89:348-355, 1927.
10. Howland, G., Campbell, W. R., Mathey, E. J., and Robinson, W. L. Dysinsulinism: convulsions and coma due to islet cell tumor of the pancreas with operation and cure. *J. A. M. A.* 93:674-679, 1929.
11. Gray, S. H., and Feinstein, L. G. Compensatory hypertrophy and hyperplasia of the islands of Langerhans in the pancreas of a child born of a diabetic mother. *Arch. Path. & Lab. Med.* 1:348-355, 1926.
12. Comfort, M. W., and Osterberg, A. E. The value of determination of the concentration of serum amylase and serum lipase in the diagnosis of disease of the pancreas. *Proc. Staff Meet., Mayo Clin.* 15:427-432, 1940.
13. Myers, V. C., and Killian, J. A. Studies on animal diabetes. 1. The increased diastatic activity of the blood in diabetes and nephritis. *J. Biol. Chem.* 29:179-189, 1917.



14. Starling, E. H. *Elements of Human Physiology*. 716 pp. Chicago: W. T. Keener & Co., 1907. P. 347.
15. Agren, G., and Hammersten, E. The behavior of crystalized secretin when digested with proteolytic enzymes. *J. Physiol.* 90:330-334, 1937.
16. Lagerlöf, H. The secretin test of pancreatic function. *Quart. J. Med.* 8:115-126, 1939.
17. Schmackpfeffer, E. S. Diss. sistens observationes de quibusdam pancreatis morbis. 48 pp. Halae: Grunerti patri ac. filli, 1817.
18. Cläßen, H. J. Die Krankheiten d. Bauchspeicheldrüse. 368 pp. Köln: M. Du Mont-Schauberg, 1842.
19. Freidreich, N. Die Krankheiten des Pankreas. In von Ziemssen, H. W. *Handbuch der Speciellen Pathologie und Therapie*. Vol. 8, Part 2. 435 pp. Leipzig: F. C. W. Vogel, 1875. Pp. 199-280.
20. Balser, W. Über Fettnckrose, eine zuweilen tödtliche Krankheit des Menschen. *Vichows Arch. f. path. Anat.* 90:520-535, 1882.
21. Fitz, R. H. Acute pancreatitis: a consideration of pancreatic hemorrhage, hemorrhagic, suppurative, and gangrenous pancreatitis, and of disseminated fat-necrosis. *Boston M. & S. J.* 120:181-187, 1889.
22. Warren, S. Adenomas of the islands of Langerhans. *Am. J. Path.* 2:335-340, 1926.
23. Frantz, V. K. Tumors of islet cells with hyperinsulinism: benign, malignant, and questionable. *Ann. Surg.* 112:161-176, 1940.
24. Guleke, N. Demonstration einer experimentell gewonnenen Pankreasnekrose. *Berl. klin. Wchnschr.* 41:682, 1904.
25. Pólya, E. A. Zur Pathogenese der acuten Pankreasblutung und Pankreasnekrose. *Berl. klin. Wchnschr.* 43:1562-1565, 1906.
26. Sweet, J. E. Surgery of the pancreas. *Internat. Clin.* 4:293-357, 1915.
27. Dragstedt, L. R., Haymond, H. E., and Ellis, J. C. Pathogenesis of acute pancreatitis (acute pancreatic necrosis). *Arch. Surg.* 28:232-291, 1934.
28. Guleke, N. Die Behandlung der Pankreasgeschwülste. In Gross, O., and Guleke, N. *Die Erkrankungen des Pankreas*. 383 pp. Berlin: Julius Springer, 1924. Pp. 312-324.
29. Whipple, A. O., and Frantz, V. K. Adenoma of islet cells with hyperinsulinism: a review. *Ann. Surg.* 101:1299-1335, 1935.
- Whipple, A. O. The surgical therapy of hyperinsulinism. *J. internat. de chir.* 3:237-276, 1938.
- Murray, M. R., and Bradley, C. F. Two island-cell adenomas of human pancreas cultivated in vitro. *Am. J. Cancer* 25:98-107, 1935.
30. David, V. C. Indications and results of pancreatectomy for hypoglycemia. *Surgery* 8:212-224, 1940.
31. Brunschwig, A. Large islet-cell tumor of the pancreas. *Surgery* 9:554-560, 1941.
32. Desjardins, A. Technique de la pancreatectomie. *Rev. de Chir.* 35:973, 1907.
33. Sauvé, L. Des pancréatectomies et spécialement de la pancréatectomie céphalique. *Rev. de chir.* 37:113-152, 335-385, 1908.
34. Kausch, W. Das Carcinom der Papilla duodeni und seine radikale Entfernung. *Beitr. z. klin. Chir.* 78:439-486, 1912.
35. Halsted, W. S. Contributions to the surgery of the bile passage especially of the common bile-duct. *Boston M. & S. J.* 141:645-65, 1899.
36. Hunt, V. C., and Budd, J. W. Transduodenal resection of the ampulla of Vater for carcinoma of the distal end of the common duct with restoration of continuity of the common and pancreatic duct with the duodenum. *Surg., Gynec. & Obst.* 61:651-661, 1935.
37. Dragstedt, L. R., Dragstedt, C., McClintock, J. T., and Chase, C. Extirpation of the duodenum. *Am. J. Physiol.* 46:584-590, 1918.
38. Mann, F. C., and Kawamura, K. Duodenectomy: an experimental study. *Collected Papers of the Mayo Clinic* 13:132-153, 1922.
39. Whipple, A. O., Parsons, W. B., and Mullins, C. R. Treatment of carcinoma of the ampulla of Vater. *Ann. Surg.* 102:763-779, 1935.
40. Whipple, A. O. Surgical treatment of carcinoma of the ampulla region and head of the pancreas. *Am. J. Surg.* 40:260-263, 1938.
41. Trimble, I. R., Parsons, J. W., and Sherman, C. P. A one-stage operation for the cure of carcinoma of the ampulla of Vater and of the head of the pancreas. *Surg., Gynec. & Obst.* 73:711-722, 1941.
42. Brunschwig, A., and Clark, D. E. Carcinoma of the intrapancreatic portion of the common bile duct. *Surgery* 10:553-562, 1941.
43. Montgomery, M. L. The influence of the external secretion of the pancreas on lipid metabolism. *Ann. Surg.* 114:441-455, 1941.
44. Dragstedt, L. R. Present status of lipocacia. *J. A. M. A.* 114:29-32, 1940.
45. *Idem*. Personal communication, 1941.
46. Whipple, A. O., Bauman, L., and Hamlin, M. Observations on the pathologic physiology of the insular and external secretory functions of the human pancreas. *Am. J. M. Sc.* 201:629-636, 1941.
47. Schnedorf, J. G., and Orr, T. G. Fifty-two proven cases of carcinoma of the pancreas and the ampulla of Vater. *Ann. Surg.* 114:603-611, 1941.
48. Kauer, J. T., and Glenn, F. Carcinoma of the pancreas. *Arch. Surg.* 42:141-155, 1941.

## FRACTURES OF THE FEMUR\*

GEORGE W. VAN GORDER, M.D.†

BOSTON

THE treatment of fractures of the femur has undergone marked evolutionary changes in this generation. The advent of the Thomas splint, the introduction of skeletal traction, the ability to treat these fractures without immobilizing joints, the employment of the Smith-Petersen nail and the use of Russell traction are but a few of the milestones that have been passed in the improved care of these fractures. And in the presence of another war, with new instruments and technics of destruction, the treatment of fractures has again changed—this time of necessity, since patients in hospitals are no longer immune from attack and frequently must be hurriedly evacuated. The most practical form of treatment of femur fractures under war conditions seems to be the insertion of fixation pins above and below the site of fracture, reduction of the fragments and incorporation of the pins in a plaster cast or Roger-Anderson steel side bar.

In civilian practice, this method has not been used routinely for two main reasons: the frequency

of infection about the pinholes, and the danger of obtaining nonunion. In war, however, conditions are so different that the advantages of a method of treatment that allows almost immediate evacuation of the wounded soldier offset many disadvantages, even serious ones.

### TREATMENT IN CHILDREN

In children under six years of age, the popularly accepted form of treatment for fractures of the femur is overhead adhesive skin traction,<sup>1</sup> followed by a plaster cast. Whether both legs or only the injured one is suspended is optional. Those advocating suspension of both legs believe that there is less likelihood of torsion of the bone fragments, whereas those who suspend only the injured leg believe that the unsuspended one can be used to better advantage as an additional counterweight.

In children over six years of age, several methods of treatment can be used effectively.<sup>1</sup> The most popular appears to be skin traction with adhesive plaster in a Thomas splint, followed by a plaster cast. Another popular method is Russell's, which

\*Presented at the annual meeting of the New Hampshire Medical Society, Manchester, May 13, 1941.

†Instructor in orthopedic surgery, Harvard Medical School; visiting orthopedic surgeon, Massachusetts General Hospital.

is described below as the procedure of choice in *intertrochanteric fractures*.

Some surgeons like Campbell<sup>2</sup> prefer to treat fractures of the femur in children by manipulation under anesthesia and application of a plaster cast. In all fairness to Campbell, it should be recorded that his results are exceptionally good, but it must also be stated that his same method in other hands has not yielded the same excellent results.

Most surgeons agree that open reduction is rarely indicated in children, since the broken femur of a child has a remarkable tendency to resume its normal shape and length if given the least opportunity. For this reason, the end results of femoral fractures in children are universally good.

#### TREATMENT IN ADULTS

##### *Fractures of Femoral Neck*

Fractures of the neck of the femur are considered emergency operative fractures at the Massachusetts General Hospital, and are treated as such. The same opinion holds true in some other well-known fracture clinics. The sooner a femoral-neck fracture is nailed, the better. This refers not only to the chances of securing bony union of the fracture but also to the patient's general welfare. In other words, if the patient's physical condition will permit, and it usually does, the operation of hip nailing is carried out at once, or as soon after the accident as possible—a matter of hours, not days.

Increasing experience with internal fixation of these fractures by means of the Smith-Petersen nail is yielding steadily improved results, so that this treatment is now universally accepted as the method of choice.

Experience has also shown that the Smith-Petersen nail is better and more efficient than Moore pins, wires or other kinds of nails in maintaining reduction, in decreasing the incidence of breaking, in migration and in the percentage of bony union obtained.<sup>1</sup>

The technic of inserting the Smith-Petersen nail, as well as the postoperative care, varies with the individual operator, and these subjects cannot be discussed in detail at the moment. Suffice it to say that the operative approach used at the Massachusetts General Hospital is through the lateral thigh muscles. A Kirschner guide wire is inserted into the femoral neck under x-ray control, and when the correct position of the wire has been obtained, a cannulated Smith-Petersen nail is threaded over it and driven home. Impaction of the fragments is the next procedure, followed by closure of the wound.

The postoperative care usually consists of one month in bed in Russell traction (for comfort),

followed by two weeks of lying free in bed, and then crutches, but no weight-bearing and no walking caliper splint. Of course, there are exceptions to this general rule.

##### *Intertrochanteric Fractures*

The ideal method of closed treatment for intertrochanteric fractures, in the opinion of many authorities, is Russell traction. Certainly, it is the most comfortable form of traction for the patient, and the most satisfactory from a nursing point of view. Its greatest disadvantage is that, to be effective, it must be carefully watched and adjusted, which means that nurses as well as doctors must understand its principles and must be able to correct any faulty mechanics that may appear.<sup>3</sup>

Russell traction accomplishes the two things desired in intertrochanteric fractures: it supplies traction in a comfortable manner with a minimum amount of weight, and it prevents external rotation of the femoral shaft by pulling through a flexed knee.

A word of warning should be sounded here: care must be taken to continue traction for ten weeks or longer, as a rule, to avoid a recurring coxa vara. Many intertrochanteric fractures buckle or sag after removal of traction. Thus, it is safer to maintain traction for a longer time and secure firm union, than to get the patient up earlier and trust in a walking caliper splint, which is nondependable.

However, a number of observers have recently noted that the mortality in cases of intertrochanteric fracture is rather high, higher certainly than that in cases of femoral-neck fracture, and this fact has led them to consider treating intertrochanteric fractures like neck fractures. These surgeons believe that the long confinement in bed with Russell traction is detrimental to health and favors pneumonia. Thus, Thornton, of Atlanta, Georgia, has devised a combination Smith-Petersen nail and plate that secures the intertrochanteric fragments in an admirable way and allows early convalescence, as in femoral-neck fractures.<sup>1</sup> The Thornton apparatus has proved its value, and can certainly be recommended in selected cases of intertrochanteric fractures. Whether it will prove suitable for all such fractures cannot yet be determined.

##### *Supracondylar Fractures*

Some clinics regard fractures of the femoral shaft as definite indications for open operation, and I think it fair to say that more and more surgeons are gradually adopting this point of view. However, the great majority of surgeons who treat fractures do not have the facilities or equipment to carry out major operative procedures on all their cases, and until they do it will be necessary

for most surgeons to continue to employ conservative measures. I believe that the operative treatment of fractures is the ideal for which one should strive, but at the present time only a handful of clinics in the United States are properly qualified to make operation the routine procedure on all fractures.

On the other hand, certain fractures should be considered definitely operative, such as those of the neck of the femur, the olecranon, the patella, extensive bumper fractures and so forth, and to these I add another—low supracondylar fractures of the femur, with marked displacement. The difficulties of controlling the bone fragments in this type of fracture by conservative or closed methods are so great as to be unjustified, and open reduction with internal fixation is the answer to the problem in my opinion.

When, however, low supracondylar fractures are badly comminuted and not suitable for bone plating or banding, nonoperative methods must be employed, and the best conservative method of treatment is the use of skeletal traction from the tibial tubercle through the knee joint, with the leg resting in a Thomas splint and Peirson attachment.<sup>1</sup>

In such cases, the Kirschner wire is made to pull through the slightly flexed knee joint in a line as nearly parallel to the plane of the tibia as possible. Thus, the traction force is transmitted through the joint with the least amount of strain on its ligaments. A common fault, and a serious one, is to flex the knee too much, which vitiates the pulling force if it is transmitted along the line of the tibia, or causes a dangerous shearing force on the joint if it is transmitted in the line of the femur.

### *Fractures of Shaft*

The most efficient closed method of treating fractures of the shaft of the femur is by means of Kirschner-wire traction in the femoral condyles, with the leg resting in a Thomas splint and Peirson attachment.<sup>1</sup>

The traction element is of the utmost importance and should be accomplished through skeletal rather than through dermal attachments. One of the lessons that long experience has taught is that traction by adhesive tape attached to the skin is neither reliable nor adequate for the treatment of fractures of the shaft of the femur, unless used in conjunction with Russell traction, when the amount of pull exerted by the adhesive tape is diminished by half because of the system of pulleys used.

Some surgeons<sup>3, 4</sup> consider Russell traction suitable and adequate for all fractures of the shaft of the femur and preferable to all other closed meth-

ods. Certainly, the method has been growing in popularity, but most surgeons of my acquaintance believe that it is suitable only for upper-third and intertrochanteric fractures—not for lower-third or supracondylar ones.

In a recent article, Lewis<sup>4</sup> states that Russell traction is the method of choice for all fractures involving the shaft of the femur and that skeletal traction should be discarded as a procedure in handling femur fractures. Such conclusions are not at all justified in my judgment, but they show that there is some difference of opinion among surgeons concerning the ideal treatment for fractures of the shaft of the femur and that Russell traction is contending for honors with skeletal traction as the method of choice.

In a recent study<sup>5</sup> of end results in the treatment of 58 fractures of the shaft of the femur by skeletal traction at the Massachusetts General Hospital, the following data were obtained: the average hospital stay of the patients was eleven and a half weeks; there were 3 cases of nonunion; shortening of the femur was present in 31 per cent, the average being 2.1 cm.; knee-joint motion was limited in 25 per cent, the average limitation being a total range of 76°; the average time that elapsed between the date of injury and the date when the patients returned to work was seven and a quarter months; and the end-result rating showed 87 per cent good, 5 per cent fair and 8 per cent poor.

### SUMMARY

Certain standardized forms of treatment for fractures of the femur are proposed, as follows: for fractures of the femoral neck, a Smith-Petersen nail; for intertrochanteric fractures, Russell traction; for low supracondylar fractures, open reduction or, if that is impossible, skeletal traction from the tibial tubercle through the knee joint in conjunction with a Thomas splint and Peirson attachment; and for fractures of the shaft of the femur, Russell traction for upper-third fractures, and skeletal traction with a Thomas splint and Peirson attachment for mid-third and lower-third fractures.

In hospitals fully equipped for operative procedures on all kinds of fractures, where fracture services are established and the treatment of fractures is considered a specialty, open reduction with internal fixation is the ideal form of treatment for all fractures of the femur in adults.

262 Beacon Street

### REFERENCES

1. Campbell, W. C., Conwell, H. E., Thornton, L., Dickson, F. D., and Shumm, H. C. Report of the fracture committee of the American Academy of Orthopaedic Surgeons: treatment of fractures of the neck of the femur by internal fixation. *J. Bone & Joint Surg.* 23:386-390, 1941.
2. Campbell, W. C. Fractures of the shaft of the femur. *Radiology* 12:106-113, 1929.

- 3 Dunlop J The Russell tract on method of treating fractures of the femur *Am J Surg* 49 155 167 1940  
 4 Lewis H M Russell tract on in the treatment of fractures of the femur *Ann Surg* 113 226 244 1941  
 5 Van Gorder G W Treatment of fractures of the shaft of the femur by skeletal traction and Thomas splint *Am J Surg* 49 149 154 1940

## DISCUSSION

A PHYSICIAN How much weight should be used in traction?

DR CHESTER L. SMART (Laconia) I should like to ask the status of the bone graft in intertrochanteric fractures. I have heard nothing about this lately, but the procedure was formerly quite popular.

DR JAMES B. WOODMAN (Franklin Falls) At our hospital we had some patients with intertrochanteric fractures to whom we applied traction by a plaster cast from the foot well up to the thigh, with the leg in full extension, plenty of padding, a little traction and a large amount of internal rotation. This position was maintained by the placing of a strip of wood on the bed at right angles to the leg under the angle, and the incorporation of the strip in the plaster cast, to maintain the internal rotation and slight traction.

It was a fairly comfortable apparatus and we succeeded in getting very good results in several cases. But I am not yet ready to report my series of half a dozen cases.

DR TIMOTHY F. ROCK (Nashua) I have seen a few cases of intertrochanteric fracture in which the Moore pin was used with good results. In 1 case, however, the pin slipped soon after operation. The other 2 patients did very well, without any additional apparatus.

DR EMERY M. FITCH (Claremont) Dr Van Gorder should be complimented on bringing to our attention the use of skeletal traction in contrast to skin traction with adhesive tape. If the former were used more, I think the results would be far better in the treatment of fractured shafts.

I should like to know a simple method of immediately reducing the fractures that slip by, I have trouble in getting them back.

DR EDGAR J. THIBODEAU (Berlin) I should like to know why patients are kept in bed for a month postoperatively. I thought the idea of the Smith Petersen nail was to get the patient up as soon as possible.

DR GEORGE W. VAN GORDER (closing) The first question concerned the amount of weight used in reducing fractures of the femur. That depends entirely on whether Russell traction or skeletal traction is used. The former procedure, as a rule, requires 10 to 15 pounds. This means, of course, that double that amount of weight is actually exerted on the femur, owing to the use of the Russell pulley system. Personally, I have never used more than 15 pounds with Russell traction, and have found this always to be adequate.

When it comes to the matter of skeletal traction in fresh fractures, one does not need to use more than 15 pounds of weight to start with, and it is customary to decrease this amount gradually. If the fracture is an old one, however, or if callus has already started to appear, the weight must be increased and can go up as far as 40 pounds.

The use of autogenous bone grafts in fractures of the neck of the femur is an important matter, but it concerns chiefly the fractures of long standing or with nonunion, rather than fresh fractures. For fresh femoral neck fractures, the percentage of excellent results following the use of the Smith Petersen nail alone is so high (80 to 85 per cent) that bone grafting as an initial procedure has not been considered necessary.

King, a well known surgeon in Australia, believes, however, that the percentage of unions in these fractures can be definitely increased by the use of a bone graft in addition to the Smith Petersen nail. Therefore, when he does his operation in a fresh case, he directs two Kirschner wires into the neck, one fairly high and the other fairly low, and over the high wire he threads a cannulated Smith Petersen nail which gives his fixation, over the lower wire he threads a  $\frac{1}{8}$  inch drill, which cuts out a smooth tunnel extending across the fracture line into the femoral head. Into this tunnel, he then inserts a well fitting graft from either the tibia or the fibula. This means that he not only has immobilized the fragments of the femur but has also bridged the fracture line with a bone graft. This operation has been done a number of times in our clinic with success, although we have employed it only in cases of nonunion.

Dr Woodman spoke of intertrochanteric fractures treated in plaster casts with a little pull. Certainly, that method seems to be a logical one if one decides to allow the patient to lie in bed for ten or twelve weeks. I have never employed traction on a leg plaster cast, because I have been afraid of exerting pressure on the dorsum of the foot where too much pressure causes pain and injury to the soft parts. The plaster cast, however, can easily control the desired positions of internal rotation and abduction. But why use any plaster at all in intertrochanteric fractures if one can use a simple method, like Russell traction that will keep the patient perfectly comfortable, allow a certain amount of moving about in bed and greatly facilitate nursing care? Russell traction prevents external rotation because it pulls through a flexed knee that is held by a hammock in the vertical plane. With the patella pointing directly upward and with the knee flexed the patient's leg is prevented from externally rotating and only half the weight that is necessary in other traction methods need be used.

Dr Rock spoke of Moore pins which might be used in intertrochanteric fractures instead of the Smith Petersen nail. That is a very practical point, and one that should be considered when open reduction of the fracture is believed to be indicated. We all know that intertrochanteric fractures are often comminuted and we also know that the cortex of the femur is not always very strong, especially near the line of fracture. Therefore, when one attempts to insert a Smith Petersen nail through the lower femoral shaft fragment close to the line of fracture, the shaft is very likely to split. To avoid this we are in the habit of cutting three small grooves in the bone with small sharp osteotomes, these correspond with the flanges of the Smith Petersen nail and, in this way, safeguard the cortex from splitting. This is also a routine procedure in the nailing of femoral neck fractures. I have never used pins in intertrochanteric fractures, and, although I can appreciate the fact that they would not have the same tendency to split the femoral shaft, I wonder if they would provide sufficient fixation of all the fractured elements. As an answer to the problem of internal fixation of intertrochanteric fractures, Thornton, of Atlanta,

devised the method that I described in my paper. This method has been successful in our hands as well as his, and the method is certainly indicated in selected cases.

Dr. Fitch asked how immediate reduction of fractures of the shaft of the femur could be accomplished. I have not been in the habit of using immediate reduction of fractures of the femur but have counted on traction, for the most part, to reduce the fragments. Sometimes, an attempt to manipulate the fragments in bed under anesthesia is successful when rather marked displacement is present. For the most part, however, the results in our clinic have been due to traction alone.

Dr. Thibodeau asked why patients with fractures of the femoral neck are kept in bed so long. The postoperative

care of these patients varies with the individual surgeon. In the Orthopedic Clinic of the Massachusetts General Hospital, we believe that a month's rest in bed is not a handicap for such a patient, because during that time, he is allowed to sit up in bed or roll over on his side and thus to move about to a certain extent. It should be noted that, with this regime, pneumonia is a very unusual complication. On the other hand, we have seen tragedies result from getting patients up too early, and there seems to be no point in forcing them out of bed on the second or third day. The idea of the Smith-Petersen nail is not so much to get the patient up as soon as possible but to render him comfortable and ensure eventual bony union of his fracture.

## MEDICAL PROGRESS

### MUMPS

CONRAD WESSELHOEFT, M.D.\*

BOSTON

MUMPS is essentially a disease of childhood. In Massachusetts, 88.6 per cent of the cases reported from 1933 to 1937 involved children less than fifteen years of age.<sup>1</sup> One attack usually affords a permanent immunity, but almost every general practitioner can cite cases of second attacks. It can occur at all ages, and it occurs throughout the year both in endemic and epidemic form. There is a tendency for the cases to increase in the cooler months, epidemics being particularly apt to take place toward the end of winter and in early spring. Actually, there is no adequate explanation of how the disease keeps going year after year. However, it is a fact that approximately nine tenths of city inhabitants above the age of sixteen have had mumps, whereas in widely scattered farming communities remote from cities a much smaller percentage of the community has had the disease at this age. In some regions, only one young adult out of ten has had mumps. This explains why pupil nurses and military recruits from the country are apt to come down with the disease within the first three months of their training.<sup>2</sup> Thus it is that a childhood disease may become a military problem of more serious import to a rapidly recruited army than to a standing army of seasoned troops.<sup>3</sup> Cities appear to be the main reservoirs of this infection. Here the virus is kept alive by active clinical cases, by subclinical cases or by actual carriers—whose existence has never been proved. So far as is known, the disease is confined to man.

The knowledge of virus diseases is still rudimentary, and it was only in 1934 that Johnson and Goodpasture<sup>4</sup> proved the existence of the virus of mumps. So far, they have shown that this filterable virus exists in the saliva during the first forty-eight hours of the disease, that it is resistant to neutral glycerin, freezing and drying, and that it can be transferred to *Macacus monkeys* through numerous generations and back again to man. The transfer to the monkey was effected by direct injection into the parotid duct. The transfer to man was accomplished by spraying into the mouths of healthy nonimmune volunteers. It is of interest that transfers were unsuccessful in summer. These experiments have been confirmed by Findlay and Clarke,<sup>5</sup> but no further progress has been made. Attempts to grow the virus on the chick embryo or by other means have so far been unsuccessful. Thus it is that, in spite of the auspicious start in the demonstration of the etiologic agent, the threads of progress must be picked up through the epidemiologic and clinical studies that have made possible a better understanding of this disease.

In spite of the establishment of the virus nature of this malady, there is still no practical diagnostic laboratory test that can stand alone, such as a positive diphtheria culture, and there is no means of bringing about an active immunity other than by acquiring the disease in its natural form. Nevertheless, progress achieved by the investigators at Vanderbilt University gives promise of advancement in both these directions. When it is realized that, in World War I, mumps stood third among the diseases causing time lost in hospital,<sup>6</sup> ranking next to venereal disease and influenza,<sup>7</sup> the

Reprints of articles in this series are not available for distribution, but the articles will be published in book form. The current volume is *Medical Progress: Annual, 1940* (Springfield, Illinois: Charles C Thomas Company, 1941. \$4.00).

\*Clinical professor of communicable diseases, Harvard Medical School; physician-in-chief, Haynes Memorial, Massachusetts Memorial Hospitals.

incentive for further research should be forthcoming.

Mumps is looked on by some today as a systemic disease, whereas it has usually been considered a local disease of the salivary glands with occasional "metastases to other organs." There is reason to believe that the portal of entry of the virus is by the mouth, but the channel by which it finds its way to the salivary glands is not known. Presumably, it is a roundabout course involving the blood stream rather than a direct one by way of the duct orifices. This newer conception is based on the long incubation period of eighteen days,<sup>8</sup> the findings in pathologic specimens,<sup>9</sup> and recent advances in other virus diseases with neurotropic properties.

Philibert<sup>10</sup> has gone so far as to propound the idea that the virus of mumps may find its way first to the central nervous system, where, being of a low neurotropic order, it tends to create little disturbance, but after an incubation period in the central nervous system finds its way through the blood stream to the salivary glands. Here, the cytotropic properties of the virus are exerted, and here it is excreted in the saliva. Although this extremely speculative hypothesis presents many flaws, one must give credit to this French author for the first serious explanation of the various sequences of events that may take place in this disease. In this way, he accounts for the facts that orchitis, ovaritis, encephalitis and pancreatitis can precede, accompany or follow the involvement of the salivary glands and that mumps can occur in these remote organs without any appreciable involvement of the salivary glands. The diagnosis in these cases is established by the purely circumstantial evidence of an exposure, the proper incubation period and the course pursued.<sup>11</sup> Philibert brings to his support the frequent finding of a pleocytosis in the spinal fluid in cases of mumps that show no clinical symptoms of meningeal irritation. There is, of course, no proof that such pleocytosis represents actual virus invasion of the central nervous system in these cases. Indeed, the virus could just as well undergo its incubation period somewhere in the lymphatic system or else, where, as seems to be a possibility in poliomyelitis, gaining access to the central nervous system in only a certain proportion of cases. Regardless of the questionable premises on which Philibert's thesis is based, it has stimulated the idea that mumps is to be looked on as a systemic disease with a variety of manifestations rather than a local disease with "complications." It is of interest to note that in a careful study of 100 cases by Greene and Heeren<sup>12</sup> nonsalivary manifestations were found in 43.

The parotid glands are involved in the vast majority of cases, and bilaterally in about 70 per cent. The submaxillary glands are frequently involved, and sometimes the sublinguals. There is clinical evidence to support the idea that infectiousness may precede the glandular swelling by at least twenty-four hours. How long this infectiousness lasts is unknown. The results of the experiments by Johnson and Goodpasture<sup>1</sup> indicate that it is of only a few days' duration, but for practical purposes a week from the onset, or for the duration of the swelling, is the usual rule for isolation.

Other glands in the body may become invaded—first of all, the gonads, especially in the male. Next in order of frequency come the pancreas, the breasts both in males and females, and the thyroid, thymus, lachrymal and Bartholin's glands.

Blood studies indicate that a normal blood picture is often present, but that a lymphocytosis is the rule. However, when glandular inflammation becomes very acute the polymorphonuclear cells tend to increase. This is especially true in severe orchitis.

The lesions within the parotid gland of experimental mumps in monkeys have been described by Johnson and Goodpasture.<sup>4</sup> There are edematous swelling of the gland and its surrounding tissue, owing to vascular injury, and parenchymal lesions, with disintegration of the acinar cells and infiltration of mononuclear cells and lymphocytes. Healing takes place by removal of the debris and regeneration of the acinar epithelium, which restores the gland without scarring. Reports on the pathologic specimens obtained from human mumps are recorded by Delater<sup>13</sup> and deLavergne and his associates.<sup>6</sup> These findings coincide with those found in the monkey. The pathology of orchitis was described by Wolbach in an article by Smith.<sup>14</sup> Manca<sup>15</sup> also gives his findings and compares the pathology with that found in orchitis from other causes.

Orchitis rarely occurs before puberty. At and above the age of puberty, the incidence is 18 per cent, but with epidemic strains there is a wide variation, which makes it very difficult to evaluate preventive measures. It was thought at one time that the virus was carried by the hand from the mouth to the penis, and that it traveled up the urethra to the testicle. This theory was disproved by the careful experiments of Radin<sup>16</sup> at Camp Wheeler. Both Dukes<sup>17</sup> and Radin have shown that strict bed rest did not reduce the incidence of orchitis. Trauma to the testicle during the incubation period and during the priortitis has been thought to precipitate testicular involvement. Dismounted drill has been recommended for the cavalry when mumps is epidemic, but the figures

given in Table 1 fail to substantiate this.<sup>18</sup> Adhering to the trauma theory, Place<sup>19</sup> advocates thigh bridges with cotton nests and suspensories; he reports a 5 per cent incidence of orchitis with such treatment, but fails to give the number of cases so treated. Equally good results have been reported without such protection with measures since proved to be ineffective.<sup>20</sup>

The administration of convalescent serum at the onset of mumps is claimed to be effective in

TABLE 1. *Incidence of Orchitis.*

PERSONNEL	CASES OF MUMPS	CASES OF ORCHITIS	PERCENTAGE OF ORCHITIS
Infantry . . . . .	1106	249	21.6
Cavalry . . . . .	162	36	22.2
Miscellaneous Army and Navy . . . . .	6576	1119	17.1
Civilian . . . . .	309	64	20.7
Totals . . . . .	8153	1468	
Percentage . . . . .			18.0

reducing the incidence of orchitis. DeLavergne and Florentin,<sup>21</sup> Cambessédès,<sup>22</sup> Odenius<sup>23</sup> and Iversen<sup>24</sup> have reported excellent results from this method, but the equally good results reported at one time from the routine use of diphtheria anti-toxin in mumps<sup>3</sup> make one hesitate to accept this treatment as one of undoubted efficacy. Convalescent serum has certainly not proved efficacious in other virus diseases when administered after the period of incubation — except in huge doses, which are entirely impractical. Thalhimer<sup>25</sup> asserts that doses of 40 to 60 cc. "will alleviate complications such as orchitis and oöphoritis," but he supplies no figures to substantiate this claim.

The treatment of orchitis consists in affording as much relief as possible by the local application of heat or cold. Some patients much prefer heat, and it has never been established that either cold or heat prevents the process from getting worse. Support to the testicles is comforting. If the condition becomes severe, all local applications are futile. Indeed, a ½ gr. of morphine may not control the pain. If allowed to go on, the pressure within the tunica albuginea becomes so great that pressure necrosis takes place and atrophy follows. One can avoid this by making an incision through the scrotum under a general anesthetic, exposing the testicle and making one or more small incisions of the tunica albuginea. Wesselhoeft and Vose<sup>26</sup> are about to report on 27 patients with mumps orchitis, 20 of whom have been followed up. In 10 severe cases operated on, only 1 patient developed atrophy; in this case, operation was performed too late to be effective. In 10 mild cases in which the patients were not operated on, no atrophy developed. Without surgical interference, the incidence of atrophy in all cases

was 54 per cent.<sup>18</sup> Consequently, the authors conclude that atrophy occurs only after severe cases, and that by early operation in such cases atrophy can be avoided.

The diagnosis of ovaritis is much more difficult than that of orchitis. Especially is this so in mild cases. Consequently, the incidence is much lower than that in orchitis. Repeated chills and marked fluctuations of pyrexia are common to both conditions. There is no limiting layer in the ovary comparable to the tunica albuginea. Therefore, any permanent damage is unlikely to occur. Daléas<sup>27</sup> and Béclere and Demange<sup>28</sup> have described the menstrual irregularities that follow mumps and ovaritis.

Prostatitis has been reported by Greene and Heeren<sup>12</sup> and also by Robinson.<sup>29</sup> Epididymitis frequently occurs with orchitis, but it may occur alone. It is less painful than the gonorrheal form and subsides spontaneously. Mastitis can occur in both the male and female, and is usually mild.

Pancreatitis is not uncommon. Farnam<sup>30</sup> and Sylvest<sup>31</sup> have reviewed the subject. Sailer<sup>32</sup> found jaundice in 4 out of 14 cases. In severe cases, the gland can be palpated through the abdominal wall. Mommsen and Mayer<sup>33</sup> and Gundersen<sup>34</sup> have discussed the possibility of mumps as a cause of diabetes. The subject offers much of interest, but the available evidence is not convincing.<sup>20</sup>

The influence of mumps on the nervous system is a subject that has come into recent prominence as a result of Philibert's<sup>10</sup> thesis. Clinical evidence of meningeal irritation occurs in 10 per cent of the cases,<sup>12, 35-38</sup> usually to only a mild degree. The findings in the spinal fluid are the same as those in preparalytic poliomyelitis. Indeed, the circumstantial evidence of mumps is the only means of differentiating the two conditions. During epidemics of mumps in the summer and fall, meningeal irritation is frequently mistaken for poliomyelitis because of the headache associated with rigidity of the neck and spine. When the encephalitis precedes the parotitis or is the only manifestation of the disease, the diagnosis hinges entirely on the circumstantial evidence of exposure.

"Latent encephalitis" is a term used to designate an increase in the cells of the spinal fluid, chiefly lymphocytes, without any clinical signs or symptoms of meningeal irritation. Silber<sup>38</sup> found a pleocytosis in 30 such cases. Finkelstein<sup>39</sup> found 6 at the Willard Parker Hospital, and in these the cell count ranged from 15 to 880. I<sup>11</sup> have reported one such case, with 400 cells per cubic millimeter. Herrick and Dannenberg<sup>40</sup> have shown that a pleocytosis may occur without signs of meningeal irritation in other infectious diseases, but the cell counts reported in these other infec-

tions never reached the numbers found in mumps. Whether this pleocytosis is really a manifestation of an encephalitis or another form of lymphocytic choromeningitis is unknown. Certainly, in poliomyelitis and in mumps, a true encephalitis may take place as determined by the pathological findings. Myelin degeneration has been found in some cases of mumps, and in others it is not in evidence.<sup>41</sup> There is a confusing note in the pathological and clinical reports on mumps encephalitis because the records frequently suggest that the attack activated an encephalitis of the lethargic or other type.<sup>42-44</sup> Especially is this so in those rare cases exhibiting spinal nerve paralyses, and when the onset follows many days after the mumps.<sup>41</sup> Donohue<sup>44</sup> in an excellent review of the subject maintains that although those cases exhibiting protracted encephalomyelitis are probably not due to the mumps virus, it is unnecessary to postulate an additional factor in all fatal cases. He reports an encephalitis that appeared eight days after a mumps proctitis. The characteristic perivascular demyelination of postinfectious encephalitis was found, but this fatal case was complicated with a confluent bronchopneumonia, and therefore can not be considered as pure mumps. Until an accurate laboratory diagnostic test for mumps is forthcoming, this question can never be settled.

Mumps encephalitis is frequently only a mild affair of a few days' duration. When there is only slight evidence of meningeal irritation, there is no necessity of doing a lumbar puncture. On the other hand, when the condition is severe, not only is a lumbar puncture indicated but spinal drainage as well, and this may have to be repeated.

Facial nerve paralyses of a temporary character have been reported.<sup>45</sup> Young<sup>46</sup> reports a unique case of bilateral optic neuritis, with complete blindness coming on thirteen days after mumps, in a ten-year-old boy who recovered completely. This temporary character of mumps neuritis is of significance in relation to mumps deafness, which is permanent. Therefore, the question arises whether the deafness of mumps should be ascribed to a neuritis of the auditory nerve. The rarity of this condition necessitates much speculation from meager facts. It is not dependent on the presence of an encephalitis. Consequently, it cannot be ascribed to a radiculitis. It may be unilateral, occurring on the opposite side from a unilateral parotitis. It may be ushered in with the acute symptoms of Ménière's disease. Mauthner<sup>47</sup> found islands of deafness in the milder cases. All this suggests that the deafness of mumps might well be attributable to damage within the cochlear, a true labyrinthitis, rather than to a primary in-

jury of the cochlear branch of the auditory nerve. The static labyrinth and the cochlear can be involved simultaneously or independently, as in the epididymis and testicle. This subject has recently been reviewed.<sup>20</sup>

There has been much discussion regarding the value of convalescent mumps serum during the acute stage of mumps. With the onset of the symptoms, the virus has already become attached to the cells of the involved organ and is well out of reach of antibodies supplied in the form of therapeutic serum. One has but to recall the enthusiasm once entertained for convalescent serum in poliomyelitis and the present lack of evidence of its value. In very large doses, convalescent serum is effective in the acute stage of measles, but only in such enormous doses as to be impractical. Since the parotitis itself rarely produces enough discomfort to warrant any such drastic measure, the question arises whether it would be helpful in combating such a condition as orchitis or encephalitis. Whether the administration of serum could prevent a mild case from developing into a severe case has not been established. Theoretically, it is unlikely that it would be of benefit, since the virus is already attached to the cells. Certainly, in severe cases, incision of the tunica and lumbar drainage are of infinitely more value as protective measures and afford prompt and genuine relief. The question whether serum administered at the onset of the proctitis prevents the involvement of other organs has been discussed above.

The prevention of mumps by the injection of convalescent mumps serum soon after exposure is an entirely different matter and is of established value. The long incubation period is of distinct advantage. Zelig,<sup>48</sup> Cambessédès,<sup>22</sup> Thalheimer,<sup>25</sup> Kutscher,<sup>49</sup> Dwyer<sup>50</sup> and Regan<sup>51</sup> have all reported protection of 100 per cent or nearly so. Brenberg and Ostroff<sup>52</sup> obtained a morbidity of 15 per cent in those given serum as against a morbidity of 39 per cent in the controls. Lyday<sup>53</sup> lost his enthusiasm for serum after injecting 86 persons in a prolonged epidemic at a children's hospital, where he obtained 11 failures, 6 of whom had re-exposures to the disease and received more than one injection of serum. Most authorities prefer serum obtained by bleeding two weeks after the disease has subsided. Persons exposed should receive the serum within a week after exposure. It is of the utmost importance to emphasize the fact that the protection afforded by the serum cannot be expected to last for more than fourteen days, and its use should be governed accordingly. It is therefore valuable as a means of preventing an epidemic but of very little value once an epidemic



is under way. This is of particular significance from a military point of view. Protective measures undertaken in schools either are entirely ineffective or, if effective, merely postpone the disease to a more disadvantageous period in life. From the standpoint of the individual and from the standpoint of national defense, there is a distinct advantage in having mumps between the ages of five and ten.

315 Marlboro Street

## REFERENCES

- Gordon, J. E., and Heeren, R. H. The epidemiology of mumps. *Am. J. M. Sc.* 260:412-428, 1940.
- Whelan, J. M., Jr. A time study of morbidity and mortality in the United States Navy. *Am. J. Pub. Health* 28:1291-1297, 1938.
- Wesselhoft, C., and Walcott, C. F. Mumps as a military disease and its control. *Mil. Medicine* (in press).
- Johnson, C. D., and Goodpasture, E. W. An investigation of the etiology of mumps. *J. Exper. Med.* 59:1-19, 1934. The etiology of mumps. *Am. J. Hyg.* 21:46-57, 1935. Experimental immunity to virus of mumps in monkeys. *Am. J. Hyg.* 23:329-339, 1936. The histopathology of experimental mumps in the monkey, *Macacus rhesus*. *Am. J. Path.* 12:495-510, 1936.
- Findlay, G. M., and Clarke, L. P. The experimental production of mumps in monkeys. *Brit. J. Exper. Path.* 15:309-313, 1934.
- Michie, H. C. Mumps. In *The Medical Department of the United States Army in the World War*, Vol. IX. Communicable Diseases, 545 pp. Washington: Government Printing Office, 1928. Pp. 451-462.
- Farnam, T. Health and medical preparedness. *J. A. M. A.* 15:49-51, 1920.
- Wesselhoft, C. Mumps: a review of our knowledge concerning its etiology, mode of transmission, incubation, and period of infectivity. *Mil. Surgeon* 46:53-62, 1920.
- deLavergne, V., Kussel, P., and Leichuman, P. Les lésions de la parotidite ouïlienne sont-elles en faveur d'une infection ascendante ou d'une infection descendante? *Presse méd.* 47:961-963, 1939.
- Philibert, A. Nouvelle conception de la pathogénie des oreillons. *Progrès méd.* 4:145-153, 1932.
- Wesselhoft, C. Mumps. In *Virus and Rickettsial Diseases, with Special Consideration of Their Public Health Significance: A symposium held at the Harvard School of Public Health, June 12-17, 1939*, 507 pp. Cambridge, Mass.: Harvard University Press, 1940. Pp. 309-348.
- Greene, J. A., and Heeren, R. H. Mumps: the incidence of palpable splenic enlargement and of "complications," and their relation to salivary gland involvement as evidence that the disease is a systemic infection. *J. Lab. & Clin. Med.* 23:129-134, 1937.
- Delater, J. Les lésions histologiques des glandes salivaires dans les oreillons. *Ann. de méd.* 11:503-503, 1922.
- Smith, G. G. Two cases of orchitis due to mumps treated by operation. *Boston M. & S. J.* 167:325-325, 1912.
- Martin, C. Über die Mumpsorchieitis. *Virechow's Arch. f. path. Anat.* 255:426-442, 1932.
- Radin, M. J. The epidemic of mumps at Camp Wheeler, October, 1917-March, 1918. *Arch. Int. Med.* 22:554-569, 1918.
- Dukes, C. The orchitis of mumps. *Lancet* 1:25, 1930.
- Wesselhoft, C. Orchitis in mumps. *Boston M. & S. J.* 183:425-430, 458-461, 491-494, 520-524, 1920.
- Place, E. H. Certain aspects of diagnosis and treatment of the contagious diseases. *Bull. New Eng. M. Center* 3:217-221, 1941.
- Wesselhoft, C. Mumps. In *The Oxford Medicine*, Vol. V. 593. New York: Oxford University Press, 1941. Pp. 487-497.
- deLavergne, V., and Florentin, P. Étude sur le pouvoir préventif du sérum des convalescents d'oreillons. *Paris méd.* 55:522-527, 1925.
- Cambessédès, H. L'emploi du sérum de convalescents dans les oreillons. *Ann. d'Hyg. N. S.* 11:83-94, 1933.
- Odenius, R. Blodsänkingsundersökningar a manskap vid Kongl. N. lands artilleriregemente, 1926-1927. *Tidkr. i mil. Hälser.* 52: 209, 1927.
- Iversen, P. Complications of epidemic parotitis and experimental treatment with convalescent serum. *Ugeskr. f. læger* 92:167-169, 1927.
- Thalhimer, W. The prophylactic and therapeutic use of convalescent serum: scarlet fever, mumps, and chickenpox. *J. Pediat.* 14:257-1939.
- Wesselhoft, C., and Vose, S. N. Surgical treatment of orchitis in mumps. *New Eng. J. Med.* (in press).
- Daléas, Ovarite ouïlienne bilatérale suivie de grossesse. *Bull. d'obst. et de gynéc.* 25:583, 1927.
- Bélère, C., and Demange, M. Ovarite ouïlienne avec hémorragies utérines fonctionnelles. *Bull. Soc. d'obst. et de gynéc.* 28:11-13, 1927.
- Robinson, W. J. Prostatic atrophy and mumps. *M. Rec.* 87:404, 1911.
- Farnam, L. W. Pancreatitis following mumps: report of a case and operation. *Am. J. M. Sc.* 163:859-870, 1922.
- Sylvest, E. Pancreatitis as complication of epidemic mumps. *Ugeskr. f. læger* 94:508-514, 1932.
- Sailer, J. Mumps. *M. Clin. North America* 3:1423-1435, 1920.
- Mommensen, H., and Mayer, I. Störungen des intermediären Kohlenhydratstoffwechsels im Verlauf des Parotitis epidemica. *Zuchts Kinderh.* 51:786-793, 1931.
- Gundersen, E. Is diabetes of infectious origin? *J. Infect. Dis.* 41: 202, 1927.
- Dopter, C. La méningite ouïlienne. *Paris méd.* 1:35-42, 1910-1911.
- Dalto, A. Reacciones meningéas de las parotiditis. *Semana med.* 40:376 and 507, 1933.
- Steinberg, I. R. Parotiditis, submaxillitis, orchitis, pancreatitis, meningitis urliana. Algunas consideraciones estadísticas. *Sem. méd.* 2:309-311, 1936.
- Silwer, H. Meningitis in mumps. *Acta med. Scandinav.* 88:355-1936.
- Finkelstein, H. Meningo-encephalitis in mumps. *J. A. M. A.* 111: 19, 1935.
- Herrick, W. W., and Dannenberg, A. M. Observations on the cerebrospinal fluid of acute disease. *J. A. M. A.* 73:1321-1328, 1919.
- Urechia, C. I., and Elekcs, N. Oreillons à forme cérébrale, à psychotique. *Bull. et mém. Soc. méd. d'hôp. de Paris* 52:1290-1936.
- Gundersen, E. Has lethargic encephalitis any relation to epidemic parotitis? *J. Infect. Dis.* 41:257-266, 1927.
- Birnberg, T. L. Mumps meningo-encephalitis. *Minnesota Med.* 18: 352, 1935.
- Donohue, W. L. The pathology of mumps encephalitis with report of a fatal case. *J. Pediat.* 19:42-52, 1941.
- McKarg, C. B., and Woltman, H. W. Neurologic complications of epidemic parotitis: report of a case of parotitic myelitis. *A. Neurol. & Psychiat.* 31:794-808, 1934.
- Young, R. C. Mumps encephalitis: report of a case with bilateral neuritis, rapid and complete blindness and complete recovery. *Orleans M. & S. J.* 86:25, 1933.
- Mauthner, O. Die Erkrankung des Nervus octavus bei Parotitis epidemica. *Arch. f. Otolaryng.* 86:223-251, 1912.
- Zehls, M. Convalescent serum in the prevention of mumps. *J. Pediat.* 1:727, 1932.
- Kuisscher, G. W., Jr. The use of convalescent mumps serum. *J. Pediat.* 16:166-170, 1940.
- Dwyer, H. L. Convalescent serum in the prophylaxis of mumps. *J. Kansas M. Soc.* 25:257-259, 1925.
- Regan, J. C. Serum prophylaxis of epidemic parotitis. *J. A. M.* 84:279, 1925.
- Barenberg, L. H., and Ostroff, J. Use of human blood in protection against mumps. *Am. J. Dis. Child.* 42:1109-1113, 1931.
- Lyday, J. H. An evaluation of convalescent serum in the prevention of mumps. *J. Pediat.* 18:473-475, 1941.

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTE MORTEM AND POST MORTEM RECORDS AS USED  
IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

### CASE 28131

#### PRESENTATION OF CASE

A nineteen year-old garage mechanic was admitted to the hospital because of a bad taste in his mouth, nausea, vomiting and abdominal pain.

The patient was quite well until about sixteen days before entry, when he returned home from skating feeling chilly and unwell. He had a slight cough, for which he took some aspirin and went to bed. The next day, he raised mucoid sputum and developed anorexia, with slight nausea. He stayed away from work, and in the next week became aware of a persistent 'bad taste' in his mouth, which he could not further describe. Thin, mucoid saliva seemed to collect in his mouth, and when he swallowed this, he became nauseated and vomited. In the week preceding entry, he continued to vomit frequently. Transient episodes of periumbilical pain appeared, coming on irregularly at any time, each lasting for only a few minutes. The pain and the vomiting were not relieved by the milk diet and bed rest prescribed by one physician, or by the "chalky" and liquid medicines prescribed by another, who diagnosed "peptic ulcer." At no time in the illness was blood coughed up or vomited, or were there any urinary symptoms, headaches or edema.

The family history was irrelevant. The patient had had nocturia (three or four times each night) all his life," always keeping a bedpan by his bed. In the nine months preceding his illness, he worked in garages, cleaning car upholstery with carbon tetrachloride. The fumes of this chemical seemed to nauseate him, making him feel faint. A week before the onset of his illness he changed jobs, to wash automobiles in a room where a spray gun using amyl acetate solvent paints was employed. He wore no mask, and complained that he often felt like vomiting.

On admission, the patient appeared well nourished but pale, weak and somewhat dehydrated. His breath was urinous. There was slight bleeding from the lower gums about the incisors. The buccal mucous membranes were pale, and the tongue was covered by a thick, dirty yellow white coat. The submental lymph nodes were enlarged, but not tender. The heart was of normal size, with a blowing systolic murmur audible all over

the precordium, loudest at the apex and over the pulmonic area. The lungs were normal. Tenderness was present in both flanks and costovertebral angles, and in the right upper quadrant of the abdomen. The extremities seemed quite weak.

The temperature was 98.6°F, the pulse 70, and the respirations 20. The blood pressure was 135 systolic, 70 diastolic.

Examination of the blood showed a red cell count of 1,900,000 with 50 gm hemoglobin, and a white-cell count of 13,800 with 89 per cent polymorphonuclears, 6 per cent lymphocytes and 5 per cent monocytes. The blood chlorides were 925 milliequiv, and the carbon dioxide combining power was 18.7 milliequiv per liter; the nonprotein nitrogen was 290 mg, the blood urea nitrogen 225 mg and the phosphorus 145 mg per 100 cc. The van den Bergh reaction was normal.

Examination of the urine showed a specific gravity of 1.015, a +++ test for albumin and a sediment with 2 or 3 white blood cells, 80 to 100 red blood cells and occasional granular casts per high-power field.

A roentgenogram of the abdomen showed one air-filled loop of intestine in the left lower quadrant, suggesting sigmoid, although a dilated loop of the small intestine could not be ruled out. Intravenous pyelograms showed kidneys of normal size and shape, with no excretion of dye over a period of forty-five minutes.

The patient was given 1500 cc of fluid intravenously. The next morning, he showed signs of periorbital edema, without swelling of the ankles. Extreme weakness and exhaustion became progressively worse during the day. Because the patient developed a Chvostek sign, he was given intravenous calcium gluconate. Following a second venoclysis, he developed signs of pulmonary edema. At this time, a roentgenogram of the chest showed fine mottling of the middle two thirds of the lower half of the lung fields, with a ground glass appearance. The heart appeared only very slightly enlarged, and the hilar vessels were of normal size. Toward evening of the second day, the pulse rose to 80, and became weaker, gradually failing. Caffeine sodium benzoate was used without avail. Death occurred at the end of the second hospital day.

#### DIFFERENTIAL DIAGNOSIS

DR ALFRED KRINES. In this patient, who had previously been in good health and who developed an illness from which he died in uremia within eighteen days, the first question one has to decide is whether this rapidly developing uremic state was due to intrinsic disease of the kidney or to some extrarenal lesion such as high intestinal

obstruction, which may simulate the uremic syndrome. This condition is occasionally called "achloremic uremia" because of the extensive loss of chlorides through persistent vomiting. Certainly, the facts as presented are consistent with such a diagnosis. In favor of it are the persistent nausea, the vomiting, the abdominal pain, the nitrogen retention and the low blood chlorides. Furthermore, there is a statement about a dilated loop of bowel. May I see the films?

There seems to be a dilated loop of bowel, but whether large or small bowel I do not know. However, it seems to me that there are more facts against the diagnosis of high intestinal obstruction than there are in favor of it. In the first place, the pain as described seems rather mild. Moreover, during the first week of the illness, there was no mention of pain at all. It appeared during the second week, seemed to be transient, lasting only a few minutes, and was not very severe. In addition, the degree of nitrogen retention seems unusually high for intestinal obstruction. Finally, the degree of anemia seems to exclude that diagnosis quite well. The patient was ill for only sixteen to eighteen days. This degree of anemia, if associated with an intestinal lesion, must have been due to rather severe hemorrhage, and there is absolutely nothing in the record to bear that out. So that I shall have to discard the diagnosis of intestinal obstruction as a cause of this uremia and assume that this was some form of intrinsic kidney disease.

The picture is entirely consistent with such a diagnosis. Many uremic patients may simulate cases of intestinal obstruction and, as a matter of fact, are not infrequently admitted from the Emergency Ward to the Surgical Service. I, myself, have seen a number of patients in uremia admitted to the Surgical Service because of abdominal pain and vomiting. Drs. Failla and Chapman<sup>1</sup> collected a group of such patients and called attention to this clinical syndrome. The clinical picture, therefore, is entirely consistent with primary renal disease. Other symptoms attracting our attention to the urinary tract are the long history of nocturia and the hematuria found on one urinalysis. The degree of nitrogen retention and anemia seems in favor of a renal lesion. I think that this patient died of nephritis. I should like to be able to stop here because that is as far as one can safely go with the information that has been given. It is always a guess to try to predict the histology of a renal lesion when one is presented with a patient dying in uremia. Uremia, regardless of the type of renal disease, is always the same, and without more in the way of clues than we have here, one must proceed on pure specu-

lation. However, I have to make some sort of histologic diagnosis.

In the first place, I cannot be sure whether renal disease was acute or chronic, since one can argue for either. In favor of a chronic lesion there are a number of factors, the first of which is the long history of nocturia, which was said to have been present during most of the patient's life. That may have been due to renal disease, but it may have been a habit that the patient developed. Many patients have nocturia of this kind without renal disease. It would have been extremely helpful to have had a urinalysis before this last illness. Also in favor of a chronic lesion is the very short duration of the final illness. It is unusual, although not impossible, for a patient to die of acute renal disease in so short a time. Most nephritic patients live a good deal longer than this. Another factor is the slight degree of anemia. Most patients with acute nephritis do not develop severe anemia in so short a period.

What are the factors in favor of an acute lesion? In the first place, the patient had always been well and had had no previous disability. The degree of hematuria recorded is more in keeping with an acute or subacute lesion than with a chronic one. Somewhat more in favor of an acute lesion is the absence of hypertension, although it is the rule to have hypertension with both acute and chronic renal disease. Acute pulmonary edema, which this patient developed, occurs commonly during the course of acute nephritis; if it occurs in chronic nephritis, it is much more likely to be associated with a fair degree of hypertension, which this patient did not have. Finally, it seems to me that the most important factor in favor of acute nephritis is the fact that the patient is stated to have had a normal-sized pair of kidneys by pyelogram. I do not know how accurate this observation is, but from what I can see in the film they look quite normal. I wish some one from the X-ray Department were here to assure me that that is an accurate observation because I am laying great stress on the fact that the kidneys were of normal size.

It would be helpful to know whether the urinary output was diminished or normal. In chronic renal disease, the nonprotein nitrogen is very much elevated with a normal urinary output, and in acute disease there is often oliguria or anuria.

DR. J. H. MEANS: The urinary output was 500 cc. on the only day it was possible to measure it.

DR. KRANES: That is not a great deal. If it was difficult to decide between acute and chronic nephritis, it seems even harder to determine the nature of the lesion. Statistically, the most likely diagnosis at this age is glomerulonephritis and

on the whole I think that the history is more consistent with an acute glomerulonephritis than with any other type of lesion. It seems to have been preceded by an upper respiratory infection, following which signs of uremia developed very rapidly. The hematuria is more in keeping with that, and as I say, glomerulonephritis is statistically the most probable diagnosis.

Another type of renal disease to be considered, and one for which there is no evidence, is acute pyelonephritis. One would not expect that to produce death in so short a time, and so far as chronic pyelonephritis goes, there is absolutely no history on which we can base that diagnosis—no chills, fever or pyuria, and a normal-sized pair of kidneys by x-ray study.

Could this have been a congenital malformation, such as bilateral megaloureters? If the patient had such an abnormality, I do not know how to do any more than guess it. There is no evidence.

Still another possibility is congenital cystic disease. No tumor masses were felt abdominally, and by x-ray examination the outline of these kidneys appeared smooth and not lobular; consequently, I must discard this diagnosis.

One other type of nephritis that should be considered is an acute tubular one on a toxic basis. The history is entirely consistent with such a diagnosis. Of course, the most common toxic nephrosis is due to mercury poisoning. If one only had a history of mercury ingestion, the rest would be easy. The salivation, the bleeding gums, the abdominal pain and the very rapid course of the acute illness are quite in keeping with acute mercurial poisoning, but one is unable to make such a diagnosis without a history of mercury ingestion. One is intrigued by the occupational hazards, in this patient. He was exposed to carbon tetrachloride over a long period. I was unaware that this substance could produce renal damage until I looked it up yesterday and found that it can produce acute renal disease, particularly when taken by inhalation, as this patient took it. In the cases I was able to find, symptoms appeared within a few hours after exposure to high concentrations of carbon tetrachloride in a closed space. If the history is correct, this patient had not been exposed for a period of a week; it therefore seems unlikely that carbon tetrachloride could have played a role in the production of this disease. Furthermore, such a severe grade of anemia is unusual. That is also true of mercury poisoning. So far as amyl acetate goes, I have been unable to find reports of renal disease produced by it. What else the patient may have been exposed to, I do not know. Lead is not a constituent of most automobile paints today.

One other possibility should be mentioned in closing. It is conceivable that when the patient developed the upper respiratory infection he took some sulfapyridine or sulfathiazole, which could produce renal insufficiency in one of two ways: by plugging the renal tubules with acetylated crystals or by producing a severe hemolytic anemia and plugging up the tubules with hemoglobin deposits. That seems far-fetched, and I merely mention it in closing.

I should say that the most probable diagnosis is an acute glomerulonephritis, although I cannot exclude the possibility of some chronic process that went on for years. The chief cause of death was the acute process.

DR. JACOB LERMAN: Aside from the diagnosis, I am interested in the treatment. Why was calcium gluconate given in the presence of a high blood phosphorus?

DR. WILLIAM M. JEFFRIES: Calcium gluconate was given for two reasons: the administration of sodium citrate and Amphogel (the former to combat the acidosis and the latter to inhibit further phosphorus absorption) had failed to produce any noticeable improvement over the previous twenty-four hours; since the patient was failing rapidly, since his pulse was not obtainable, his cardiac rhythm was grossly irregular at a rather slow rate, and there were numerous muscular twitchings, we gave intramuscular caffeine to stimulate the heart and intravenous calcium gluconate to combat the muscular twitchings and low serum calcium and to control the cardiac irregularity, which might have been due to calcium deficiency. Fishberg<sup>2</sup> mentions that the tetaniform muscular twitchings and spasms of uremia can often be stopped almost instantaneously by the intravenous administration of calcium gluconate or chloride. In the case under discussion, we gave gluconate rather than chloride because of the presence of acidosis.

The temporary improvement following this treatment was quite striking. Within five minutes, the cardiac rhythm became regular, the pulse was stronger, the muscular twitchings stopped, and the patient responded to questioning. This condition lasted for about two hours, but then he again started failing rapidly, and in spite of further administration of caffeine, death occurred within a few minutes.

Of course whether the calcium helped restore the cardiac rhythm to normal is questionable, since the caffeine may have been responsible for this, but the twitchings were certainly helped, and we saw no evidence that the calcium had done any harm.

## CLINICAL DIAGNOSES

Glomerulonephritis (? acute, ? subacute, ? chronic).

Secondary anemia.

Uremia.

## DR. KRANES'S DIAGNOSES

Acute glomerular nephritis.

Uremia.

## ANATOMICAL DIAGNOSES

Nephritis, acute glomerular.

Pulmonary hemorrhage, bilateral, marked.

## PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: The kidneys were slightly enlarged, weighing 350 gm. The surfaces were slightly pale and dotted with minute petechial hemorrhages. The histologic picture was characteristic of acute glomerulonephritis, with marked proliferation of the capsules and almost no scarring of the tufts. There was beginning lipoid degeneration of the tubules. It was a very acute lesion, consistent with three weeks' duration. The heart was rather small, weighing 250 gm. There was no pericarditis. There was a severe grade of hemorrhagic pulmonary edema with a histologic picture essentially like that of Case 28112,<sup>3</sup> in which it was much more diffuse, however. There was the same marked hemorrhage into the alveoli and the formation of plugs of fibrous tissue, even in this short period, which obliterated a great many of the minute branches of the bronchial tree.

DR. KRANES: Do you not think it is quite unusual to develop such a severe grade of anemia in so short a time?

DR. MALLORY: I can remember only one case of acute nephritis that had an anemia nearly so severe as this. This was in a boy of about ten in whom, as I remember, the red-cell count dropped to 2,000,000 in the course of a few weeks. The bone marrow in the present case was entirely nonspecific, — neither hypoplastic nor hyperplastic, — which is about what one would expect in a case of nephritis. There was nothing to suggest any underlying blood disease to explain the anemia, so that I am forced to conclude that it was probably on the basis of nephritis.

DR. KRANES: Did you find any reason to suspect that poisoning played a role?

DR. MALLORY: None whatever.

A PHYSICIAN: How do you account for the nocturia?

DR. MALLORY: Habit, I guess.

## REFERENCES

- 1 Tailla, S. D., and Chapman, F. M. Paralytic ileus and intestinal obstruction simulated by disease of the urinary tract. *Virginia Med Monthly* 67:368-372, 1940.
- 2 Fishberg, A. M. *Hypertension and Nephritis*. Third edition 68 pp. Philadelphia: Lea & Febiger, 1934. P. 145.
3. Case records of the Massachusetts General Hospital (Case 28112) *New Eng. J. Med.* 226:459-463, 1942.

## CASE 28132

## PRESENTATION OF CASE

A twenty-five-year-old Greek housewife was admitted to the hospital because of increasing abdominal distention of several months' duration.

A year and a half before entry, she was operated on in another hospital because of "abdominal pains." She was told that "no tumor was found, but a cyst was removed." There was abatement of the pains. Some months after this operation, the patient developed transient jaundice, with clay-colored stools, pain in the right upper quadrant, nausea, vomiting and fever, apparently associated with intolerance for fatty foods. This attack cleared without medication or hospitalization. Nine months before entry, the patient experienced a similar episode. After this, she remained on a low-fat diet. Two and a half months before entry, she noted some distention of the abdomen, especially on the right side, without reappearance of any of her previous symptoms. After a month and a half, the distention became more generalized, and there was some constipation. The menses were regular until three months before entry, when there was slight dysmenorrhea, with an otherwise normal period. Two episodes of metrorrhagia occurred in the next month, and normal periods were then resumed. Finally, about a week before entry, the urine was "Coca-Cola colored" for three or four days. There was no weight loss during this illness.

The patient had been married several years without pregnancies. She lived in Greece until the age of thirteen. At the age of eleven or twelve, she had an undiagnosed sickness characterized by high fever. At that time, her diet included goat's milk, and she was in close association with sheep and other cattle. The family history was irrelevant.

On admission, the patient appeared thin faced, with slightly yellow skin and scleras. The heart and lungs seemed normal. The abdomen was swollen and tympanitic, with liver dullness extending several fingerbreadths below the costal margin. There was no evidence of peritoneal fluid.

The temperature was 99°F., the pulse 90, and the respirations 20. The blood pressure was 120 systolic, 88 diastolic.

Examination of the blood showed 1 red cell count of 3,700,000 with 93 gm hemoglobin, and 1 white cell count of 10,300 with 20 per cent polymorphonuclears, 23 per cent small lymphocytes, 2 per cent monocytes, 53 per cent eosinophils and 2 per cent basophils. No parasites were seen in the blood. The blood Hinton reaction was negative. The urine showed a + test for albumin and a sediment with 200 white blood cells, scattered and in occasional small clumps per high power field. Bile pigment was present in the urine in two out of three examinations. The stools showed no parasites or occult blood in six examinations.

A roentgenogram of the chest showed no positive evidence of disease. A roentgenogram of the abdomen showed a large dense mass filling the right side and extending down below the crest of the ilium. This mass seemed contiguous with the liver, and through it could be seen a normal kidney shadow. The spleen was not visualized.

On the second hospital day, an operation was performed.

#### DIFFERENTIAL DIAGNOSIS

DR HOWARD ULFELDER. In essence, we are presented with the case of a young married woman who was chronically ill and had noted increasing abdominal girth. Whether this represented an actual intra-abdominal mass we are not told. On physical examination, the abdomen was swollen and tympanitic, with liver dullness extending several fingerbreadths below the ribs. The x-ray report, however, was less noncommittal, stating that a dense mass filled the right side and seemed contiguous with the liver.

Let us assume that this was an intra-abdominal mass. What facts help localize the site of its origin? In the first place, we are told that the patient had an operation a year and a half previously. This could lead to endless conjecture, but I shall trouble with none of it. We do not know what the operation was or what was found or done. The patient had obviously been ill for a year and a half. Following this, she had symptoms that pointed definitely to the right upper quadrant. She had an attack of pain, with jaundice, vomiting, nausea and some fever, which was repeated nine months before entry. Presumably, she also had jaundice with the second attack. She was able to control the symptoms, however on diet alone, and it was not until two and a half months before entry, when she noticed gradual distention of the abdomen, that she became sufficiently preoccupied with her condition to come in and have something done about it. She had some jaundice on entry—chronic jaundice, I assume.

Are there any other facts that help us to find out what might cause a mass in or very near the biliary tree in a young married woman? We know that she was a Greek and had lived in Greece until she was thirteen. We note—in fact, it is specifically brought out—that she was in close association with cattle in her childhood. This, together with the marked eosinophilia, makes me believe that some parasitic infestation explains the disease, and the most likely one is the echinococcus. I therefore believe that the diagnosis in this young woman is hydatid cyst of the liver.

Can we localize it further? Have we the x-ray films?

DR TRACY B. MALLORY. We have the x-ray films but no radiologist to interpret them.

DR ULFELDER. We note that the diaphragm is not unduly elevated on the right side nor is there the tenting that is usually described in echinococcal cyst near the superior surface of the liver. The fact that the mass extends so far down into the abdomen,—it is described as reaching the iliac crest,—makes us believe that the mass is therefore in an unusual site, namely, the inferior aspect of the liver. Echinococcal cyst is said to occur most often in the right lobe, but in the right lobe more frequently near the superior interior aspect. It is conceivable that the great size of the mass is due to the fact that it occupies a somewhat more distensible structure, such as the gall bladder, and I toyed with the idea of hydatid cyst of the gall bladder. However, I believe that the diagnosis is hydatid cyst of the right lobe of the liver.

One final point the very high eosinophilia is said to be some indication that the cyst is actually draining. In other words, some form of allergic reaction is being produced in the body by the products of this parasitic infestation, and I therefore hazard the guess that the echinococcal cyst was so near the biliary tree that it actually spilled out daughter or granddaughter cysts into the common bile duct and hence into the gastrointestinal tract.

DR EDWARD B. BENEDICT. I peritoneoscoped the patient. The findings were as follows:

The entire upper abdomen was occupied by a firm comparatively smooth but uneven mass, parts of which were pearly grey in color, and parts of which were covered with numerous blood vessels. The lower border of which on the right side was smooth and rounded and extended about 4 cm below the umbilicus. On the left side it extended on a level with the umbilicus. The border of the liver on the left side was clearly seen being distinct from the mass and overlying it. It appeared sharp and normal, and its anterior surface showed no implant. On the right side, however it was impossible to distinguish the liver edge, the mass

appearing practically contiguous with it. The patient was so tender on the right side that examination was difficult. The gall bladder could not be seen owing to the mass. The right lobe of the liver appeared irregular and uneven. Some areas suggestive of metastatic disease were seen in the right lobe of the liver. There was a small amount of free bloody fluid in the pelvis. The patient was put in Trendelenburg position. A nodule, about 1 cm. in diameter and characteristic of metastatic disease, was seen in the cul-de-sac, surrounded by a half dozen small, pin-point implants suggestive of ovarian cancer. A biopsy was obtained from the large implant.

DR. MALLORY: Do you want to give your impression after peritoneoscopy?

DR. BENEDICT: My impression from the implant was that we were dealing with a malignant process.

DR. MALLORY: The specimen that Dr. Benedict obtained was sent to the laboratory, where we found that it consisted of fibrous tissue with many giant cells in it. We were unable to make any definite diagnosis and reported it as a granulomatous inflammatory process.

Do you want to add to or change your diagnosis, Dr. Ulfelder?

DR. ULFELDER: No; except that I might alter my opinion that it might have been spilling into the common duct and say instead that it was spilling into the free peritoneal cavity.

#### CLINICAL DIAGNOSIS

Echinococcal cyst?

#### DR. ULFELDER'S DIAGNOSIS

Echinococcal cyst.

#### ANATOMICAL DIAGNOSIS

Echinococcal cyst.

#### PATHOLOGICAL DISCUSSION

DR. MALLORY: A spilling into the peritoneal cavity had undoubtedly occurred. It was considered impossible to make a positive diagnosis without exploration, which was eventually done.

Dr. Leland S. McKittrick, who operated on this patient, found a very large cyst that had ruptured and was the site of a marked inflammatory process. However, it was quite possible to recognize it grossly, and later histologically, as an echinococcal cyst. It was much too large and too deeply embedded for removal, and he was forced to marsupialize it. The patient has had considerable relief of symptoms, but when she was discharged to a convalescent home she was still not what one could call well.

A PHYSICIAN: How about the gall bladder?

DR. MALLORY: It was normal.

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established in 1828

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND  
PUBLISHED UNDER THE JURISDICTION OF THE  
COMMITTEE ON PUBLICATIONS

Official Organ of

THE MASSACHUSETTS MEDICAL SOCIETY  
and

THE NEW HAMPSHIRE MEDICAL SOCIETY

## EDITORIAL BOARD

Joseph Garland, M D	Stephen Rushmore M D
William B. Breed, M D	Henry R. Viets, M D
George R. Minot, M D	Robert M. Green, M D
Frank H. Lahey, M D	Charles C. Lund, M D
Shields Warren, M D	John F. Fulton, M D
George L. Tobey, Jr., M D	A. Warren Stearns, M D
C. Guy Lane, M D	Dwight O. Hara, M D
William A. Rogers, M D	Chester S. Keefer, M D

## ASSOCIATE EDITORS

Thomas H. Lennan, M D	Donald Munro, M D
Henry Jackson, Jr., M D	

Walter P. Bowers, M D, EDITOR EMERITUS  
Robert N. Nye, M D, MANAGING EDITOR  
Clara D. Davies, ASSISTANT EDITOR

SUBSCRIPTION TERMS: \$600 per year in advance, postage paid, for the United States (medical students, \$350 per year); Canada, \$704 per year, Boston funds, \$852 per year for all foreign countries belonging to the Postal Union.

MATERIAL for early publication should be received not later than noon on Friday.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston, Massachusetts.

## FINANCING THE WAR

We have accepted the challenge of the Axis forces. We will uphold our fight for freedom with all the resources of America. New England's production lines, like those the Nation over, are turning out more and more war matériel and equipment. Old factories are now making new tools of war. New armament lines are being built. This year, the total bill for the war effort will exceed \$60,000,000,000. Next year, it may be even higher. Victory is the goal—no matter how great the cost. And we as individuals must share the financial load.

We are paying higher taxes than ever before, but even a Victory Tax program falls far short of the amount required to meet the annual cost of war. A part of the money will be obtained from

banks and other lending agencies, but this does not make up the deficit. The Government must secure billions of dollars by borrowing directly from the people.

The Treasury Department offers United States Defense Savings bonds and stamps within the purchase range of all Americans. The largest bond costs \$10,000, the smallest stamp, 10 cents. This is the people's investment program—through which we, as individuals, invest our dollars in the war effort. At the same time, such investments build toward our own future security and can be drawn on in case of emergency.

There are three series of United States Defense Savings bonds. Series E bonds may be bought only by individuals and can be obtained at any post office and almost any bank. A bond of this series may be registered in the names of two persons or in the name of one, with a second listed as beneficiary. The smallest costs \$18.75 and pays \$25.00 at the end of ten years. Series F bonds are also appreciation bonds, but these can be purchased by associations and corporations, as well as by individuals. They cost 74 per cent of their face value, and the Government pays back the full face value at the end of the twelve-year maturity period. The smallest bond of this series costs \$18.50, and the largest, \$7400. The Series G bonds cost the same as their face value and pay interest semiannually at the rate of 2½ per cent. They mature in twelve years, and are issued in denominations from \$100 to \$10,000. Although bonds of Series F and G are issued only by Federal Reserve banks and the Treasury Department, most commercial banks handle applications for them.

Our forefathers fought to secure the freedoms of the American way of life. We, physicians of the present generation, must face the crisis of world conflict with the same unflinching spirit, whether this means service with combat troops, in base hospitals or among civilian communities. In addition, we must buy, and continue to buy, United States Defense Savings bonds and stamps. Our dollars must do their part in the forward march to Victory.



## THE INDUSTRIAL NURSE

INDUSTRIAL absenteeism due to accidents and disease accounts annually for tremendous losses in production, as well as financial losses to employers and workers. In reducing this drain, which eventually affects the whole community, the industrial nurse can serve in a vital role. Although in large plants the workers' health problems are supervised by a physician, the nurse working under him carries heavy responsibilities in any health program. She has valuable personal contact with the individual worker and knows just what his work is and, thus, his exposure to injurious substances or dangerous conditions. Such knowledge may be of great value to all concerned if a question of compensation arises. In her daily contact with the employees, she has an opportunity to detect symptoms or conditions that may be forerunners of more serious concern if allowed to go untreated—a respiratory disease, a dermatitis or cuts and abrasions that the worker may consider too unimportant to warrant medical care. Furthermore, she may be acquainted with the employee's home environment and with other outside factors that might affect his work or health. She is familiar with local social and health agencies that can be turned to for help in special problems. The well-trained, alert and tactful nurse can frequently supply the physician and employer with information about a worker that could be gained through no other medium. Actually, her position is that of liaison officer between the worker, the physician and the management.

If the nurse's responsibility in large plants is great, it is doubly so in small factories, where the great percentage of workers are to be found and where conditions may be very poor. Since a physician for such a plant is usually in attendance for only a few hours each week, he cannot be expected to know in detail the type of work performed by the workers, still less the workers themselves. Here the nurse is an invaluable source of information on special prevailing conditions and on such a matter as the introduction of new materials and processes entailing possible danger.

In a small factory, far more than in a large plant, the nurse must be a propagandist to employee and employer alike, and must work single-handed for simple hygienic measures, safety programs and the general principles of occupational health.

Morbidity rates for working men are higher—frequently far higher—than those for the general population, and it becomes obvious, now if never before, that the worker's health is of immediate concern to the Nation. The industrial nurse is as important in the present war as her sister with the Services, and every effort should be made to use her more extensively and to increase her responsibilities.

### BIBLIOGRAPHY

- Bloomfield, J. J. The responsibility of the nursing profession in industrial hygiene. *Pub. Health Rep.* 56:1131-1141, 1941.  
 Hubbard, R. W. Industrial nursing. *Am. J. Pub. Health* 30:1224, 1940.  
 Kuechle, B. F. The industrial nurse: her responsibility in the efficient administration of a compensation law. *Indust. Med.* 10:150-152, 1941.

## MEDICAL EPONYM

### NEGRI BODIES

The results of the studies made by Adelchi Negri (1876-1912) as an assistant in Golgi's pathology laboratory at Pavia were first presented before the Società Medico-Chirurgica at Pavia, March 27, 1903. "Beitrag zum Studium der Aetiologie der Tollwuth [A Contribution to the Study of the Etiology of Rabies]" appeared in *Zeitschrift für Hygiene und Infektionskrankheiten* (43: 507-528, 1903). A portion of the translation follows:

The phenomenon to which I wish chiefly to direct attention is first the occurrence of a peculiar microorganism in the nervous system of rabid animals; everything leads us to believe that this is to be considered a protozoon. . . . Almost always, the favorite site for the microorganism is the Ammon's horn—always if the infection is subdural. In this region, especially in the larger nerve cells, the parasites are present in large numbers.

In a paper, "The Etiology of Rabies: The diagnosis of rabies on the basis of new discoveries," which was read before the Società Medico-Chirurgica at Pavia, July 14, 1903, and appeared in the above journal (44: 519-540, 1903) under the title, "Zur Aetiologie der Tollwuth: Die Diagnose der Tollwuth auf Grund der neuen Befunde," Negri made the following statement:

On the basis of my studies, I have concluded that this microorganism, which is found solely in the nerve cells of the rabid animals, is the specific exciting cause of rabies.

R. W. B.

## MASSACHUSETTS MEDICAL SOCIETY

## SPECIAL MEETING OF THE COUNCIL

A special meeting of the Council of the Massachusetts Medical Society will be held in John Wire Hall, Boston Medical Library, 8 Fenway, Boston, on Wednesday, April 15, 1942, at 10:30 a.m., at the direction of the president, Dr. Frank R. Ober.

**Business** To receive and act upon the report of the Committee to Revise the By Laws.

MICHAEL A. TIGHE, MD, *Secretary*

Councilors are asked to sign one of the two attendance books before the meeting. The Cotting Luncheon will be served.

Dr. Ober requests that all councilors remain until the end of the meeting.

## COMMITTEE ON MATERNAL WELFARE

CASE HISTORY: ECLAMPSIA, FOLLOWED BY FATAL CEREBRAL HEMORRHAGE

A twenty-three year-old primipara was first seen at the beginning of the seventh month of pregnancy. From then on, her care was excellent. When she was about eight and a half months pregnant, albuminuria and a blood pressure of 160 systolic, 90 diastolic developed, and she was hospitalized. The past history was irrelevant. Physical examination and the blood Wassermann reaction were negative. The pelvic measurements were normal. The usual treatment for toxemia was instituted, and the systolic blood pressure ranged from 140 to 160, with persistent albuminuria. Labor was not induced and did not begin until three weeks after the expected date. At the end of four and a half hours of labor, the patient was seized with convulsions and died undelivered. Autopsy revealed massive cerebral hemorrhage, with typical findings of eclampsia in the liver and the other viscera.

**Comment.** This patient was under hospital observation for three weeks, and it is very evident that at no time was she considered seriously ill. The record does not state just what the treatment for toxemia was. Many similar patients put on a skimmed milk diet of  $2\frac{1}{2}$  quarts daily, with nothing else to eat and with a recorded twenty-four hour urine output, show in a few days a lowered blood pressure, a diminution in edema, which this patient is said not to have had, and in the amount of albumin, and an increased twenty-four hour output. It is, of course, probable that had labor been induced when no improvement occurred, this fatality would have been prevented, and it is very possible that a vaginal examination when the patient was at estimated term would have revealed a cervix favorable for induction by rupture of the membranes.

Continued albuminuria and sustained blood pressure for three weeks can certainly do no good, and undoubtedly may cause kidney damage. Massive cerebral hemorrhage following so soon after convulsions is very unusual. The autopsy proved that this fatal complication may occur in a patient who has been showing only moderately increased hypertension. Hence, conservatism, which was the cause of this patient's death, can be carried too far.

## FAMILY NUTRITION AND DEFENSE\*

We all know that real defense is not only "for" the people but also "by" the people. The main job of all Americans is to build a strong America. For this, we depend on many important products like rubber and steel. However, it also takes men strong, husky ones, to work as well as to fight. Behind them stand millions of other Americans—large and small, old and young—willing to take an active part in this immense, undertaking.

Building men takes years. It is accomplished with such simple things as the right food, plenty of sleep, sunshine, fresh air, active work and play. Strength, stamina, nerve and grit come with robust health. The nation needs families where every member—from baby to grand parents—is in top notch buoyant health.

How about yourself and your family? Are their bodies well developed (not too thin, or too fat), their muscles firm (not flabby), their teeth sound (not decayed), their eyes bright (no dark circles), their skins clear (with good color), their hair glossy (not brittle), their postures alert and self-confident (not drooping), their appetites and digestions good (not finicky), their dispositions happy and fun-loving (not irritable and highstrung, or listless and seemingly lazy) and their endurance and vigor high?

Is there some point on which you could improve? Keeping fit is not always easy, but it is much cheaper and far simpler than getting back your pep after illness or overfatigue. It ensures greater physical vigor, sturdier nerves, clearer thinking, better resistance to disease and increased ability to turn out a good day's work—all very necessary for all of us, whether we are in the service, in industry, in school or at home.

America can become a nation of husky, well-nourished people, she has the food, the knowledge and the will to do it. It takes farmers, manufacturers, distributors, grocers—everyone.

We must know which foods are most economical to each member of the family, and how to buy these foods wisely and serve them tastefully.

We must also learn how to spend our money economically to get the greatest amount of protective foods—milk, eggs, fruit and vegetables—that our budget will allow, even though the costs of living go up.

Furthermore, we must care enough about the health and nutrition of ourselves and our families to change poor habits for good ones. We should learn to like all the foods that are on the A-1 list, those "priorities in nutrition." We should get to bed in time to get up in time for a good breakfast, instead of hustling off with just a swallow of coffee. We should plan our day's work and leisure so as to have time to relax and get a good night's sleep.

\*A "Green Lights to Health" broadcast given through Station W A B by Dr. M. Louise Drex on Saturday January 24 and sponsored by the Public Education Committee of the Massachusetts Medical Society and the Massachusetts Department of Public Health.

Much of the defense program can be carried on only by experts. But here is a vital part that is up to each individual, and he alone decides how well it will be done. There are no medals, no glamour, no special citations for bravery, and it may seem humdrum. Remember, however, it is important. It does make a difference. Even your own personal efforts benefit not only you, but your family and community. Good nutrition puts more life in living. It depends on a few simple foods—for what we eat makes a great deal of difference in how we look and how energetic we feel. Choosing the most valuable foods means knowing which ones to buy, then being sure to eat your share of them at three good meals each day. (And a word about meals—take your time; don't rush—you'll enjoy them better and digest them more easily. Also, make mealtime a happy time, with no quarrels or disciplining.)

No matter whether you can afford to spend \$5.00 or \$6.00 apiece for food for each member of your family each week, or only \$2.50—all can be well fed. The pattern for choosing these foods is the same. It includes plenty of building material for strong bodies, minerals and vitamins for top-notch health, and calories for energy. Whether it costs a great deal or a little depends on whether your family has expensive tastes or enjoys the more economical foods, how thrifty you are in your shopping, and how good a cook and manager you prove to be.

The first and foremost need at any age is milk—three or four cups for children and two cups for adults—in one form or another, bottled or evaporated. Drink it plain, or as a milk shake, in cream soup, custard, pudding and ice cream and on cereal; or, perhaps, as cheese in a sandwich or salad, in macaroni or with gingerbread or crackers. The least expensive cheddar cheeses are as valuable as our former imported kinds. And evaporated milk mixed with an equal amount of water is equal to regular milk and costs less. It is fine for most recipes that call for milk.

Vegetables are a second need: one or more servings of white or sweet potato especially baked, boiled in the skin or mashed, and two servings of other vegetables, one of which is raw, if possible (it may be "second helping" on the same vegetable occasionally, if necessary). Green, leafy and bright-yellow ones are the more valuable, especially greens, carrots, tomatoes (fresh or canned), green peas and beans. Cooked, canned or frosted vegetables are about equal in food value so long as the juice in which they are cooked is used for soup, gravy or cocktails. Save food value by being sure your vegetables are not overcooked. Season them well and serve them in different ways to tempt your family.

Fruits are also essential, two servings, one of which is raw, especially oranges, grapefruit and berries. Fresh, canned and dried fruits are all good at any meal, or for snacks, and even in sandwiches, or as sweets in place of candy. It costs more to buy fruits and vegetables when they first appear in the market, but they are apt to be very reasonable only a few weeks later, so that it often pays to wait a little.

Use one egg a day, or at least three or four each week for each person. Serve at any meal, either plain or in foods like puddings, custards, salads and sandwiches. All eggs have the same food value, whether white or brown shell, local or Western: the color depends on the breed of hen, and freshness is often decided more by how cold the egg has been kept, than by how long it has been kept. Using cold storage eggs for cooking is good economy when your pocketbook is slim.

One daily serving of meat or fish is necessary. Dried

beans or peas, extra cheese, eggs, fish and peanut butter are substitutes if we cannot afford meat every day. Live (beef, pork, lamb or calf) stands at the head of the list. Eat it often. Most of the inexpensive meats and fish have as much food value as the costly ones. These meats may take more cooking, but often have better flavor. It is expensive to buy ready-cooked meats, unless your time is very precious. Many of the cheaper sausages and frankfurters, although low in price, have less real "meat value" than other low-cost meats.

Bread and cereals are vital. At least half the bread used should be dark,—rye, whole wheat, Graham and so forth,—and the rest made with enriched flour. Use dark cereals like oatmeal, rolled wheat, malted breakfast foods and shredded wheat, instead of white ones. Flakes and puffed kinds cost much more, when the number of servings in a package is considered.

Use butter on bread and vegetables as generously as your pocketbook allows. Vitamin A oleomargarine is almost as valuable and much cheaper than butter at present, but peanut butter is a good spread. Other fats are less necessary, since they supply only calories and no vitamins.

Regarding molasses and sweets, brown sugar gives you the most for your money and should be used often in place of white sugar. Simple desserts and sweets can be used in moderation and at the end of a meal, not to take its place. A sundae or a bar of candy is not equal to a meal, even if it satisfies hunger easily.

If your food money must be carefully stretched, remember that a fussy, finicky family is expensive to feed. Start them early to learn the fun of trying new things. Anyone can learn to like most foods if he tastes a little bit at first and tries it from time to time in weeks to come. Furthermore, eating out at restaurants and tea rooms and even extra snacks at the soda fountain run into money if they get to be a habit. If you entertain at home often,—either simply or in "bang-up" style,—your food budget will feel the strain unless you make allowances for this ahead of time.

Do not be satisfied to stop with the nutrition of your own family (although this is your first responsibility, of course). Help promote a good nutritional program for the whole community. All this takes courage and hard work. Such things are not easy to do in busy days like these. But they will be done by all who wish to build the defenses of America, with a virile civilian force as well as a strong fighting force, able to stand the gaff of everyday life, with power and assurance.

Write to the Massachusetts Department of Public Health at 73 Tremont Street, Boston, for more details if you are interested in nutrition and defense.

## DEATHS

BROWN—GEORGE A. BROWN, M.D., of Barre, died March 15. He was in his eighty-fifth year.

A native of Barre, Dr. Brown received his degree from Columbia University College of Physicians and Surgeons in 1883. He was a member of the Massachusetts Medical Society and the American Medical Association.

He is survived by his widow, two sons and two daughters.

CLARKE—INEZ L. CLARKE, M.D., of Cambridge, died recently.

Dr. Clarke received her degree from Tufts College Medical School in 1904. She was a member of the Massachusetts Medical Society and the American Medical Association.

**MUTTY**—**LAWRENCE T. MUTTY, M.D.**, of Wicahitum died February 25. He was in his thirty-seventh year. Born in Bangor, Maine, Dr. Mutty received his degree from Middlesex University School of Medicine in 1931. He was a member of the Massachusetts Medical Society and the American Medical Association.

He is survived by his widow, a son and a daughter.

**PETERS**—**ANDREW PETERS, M.D.**, of Longmeadow died January 8. He was in his fifty-second year. Born in Lake George, New York, Dr. Peters received his degree from Columbia University College of Physicians and Surgeons in 1914. He was a fellow of the Massachusetts Medical Society and the American Medical Association.

His widow, two sons and a daughter survive him.

## WAR ACTIVITIES

### CIVILIAN DEFENSE

#### TEXTBOOK ON WAR GASES

*Protection against Gas*, a textbook on war gases to be used for instruction of public employees and volunteers enrolled in the various groups of civilian defense workers has been issued by the United States Office of Civilian Defense. The book was prepared by the War Department under the direction of the Chief of Chemical Warfare Service, United States Army, with suggestions from the National Technological Civil Protection Committee, a special advisory committee of engineers. The section, *First Aid Treatment of Gas Casualties*, was prepared with the assistance of the Medical Division of the Office of Civilian Defense.

Although war gases have been used only once in this war, so far as is known, it is essential that thorough preparation be made to deal with them. Several groups of state and local officials have already had training in the Civilian Defense School conducted by the Chemical Warfare Service at Edgewood Arsenal, Maryland. Graduates of this school are returning to their homes to instruct others in the identification of gases, measures for protection and methods of decontamination.

The 75-page manual contains descriptions of the principal gases, their effects and the first-aid measures to be used in the care of persons who have been subjected to gas attack. Methods of individual protection, which include the use of masks and the wearing of protective clothing, and methods of collective protection, such as use of gas-proof shelters and methods of decontamination, are described. There is a chapter on the protection of animals, especially horses and homing pigeons.

## NEW HAMPSHIRE MEDICAL SOCIETY

### DEATHS

**HINDS**—**WILLIAM H. HINDS, M.D.**, of Milford died March 10 in Wilton, where he had been ill for several weeks. He was born in Milford, July 22, 1867, the son of Dr. W. H. Hinds and Harriet M. Hinds. He graduated from Boston University School of Medicine in 1895, after which he was associated with his father in general practice in Milford until the latter's death.

Dr. Hinds was long prominent in the Masonic fraternity. For many years he was the school physician in Milford and Amherst. He was a member of the New Hampshire Medical Society and the American Medical Association.

**LA FRANCE**—**ALBERT J. LA FRANCE, M.D.**, of Laconia, died at home on March 12, after a long illness. He was in his seventy-first year.

He graduated from Bowdoin Medical School in 1896. He was on the original medical staff of the old Cottage Hospital at Laconia, and was a member of the Belknap County and New Hampshire societies, the American Medical Association and the American Ophthalmological Society.

Dr. LaFrance is survived by his widow, Mrs. Caroline J. LaFrance, a daughter, Mrs. Dorothy Brockington, of Buffalo, New York, a son, Dr. A. Philip LaFrance, of Laconia, and a brother, Edward LaFrance, of Gloucester, Massachusetts.

**WEBBER**—**NORMAN B. WEBBER, M.D.**, of Manchester, died suddenly on February 22. He was in his sixty-eighth year.

Dr. Webber graduated from University of Vermont, College of Medicine in 1903. He was a member of the New Hampshire Medical Society.

## MISCELLANY

### ILLUMINATION OF TUBERCULOSIS IN CIVILIANS AND IN MEMBERS OF THE ARMED FORCES

We are all in it, said the President the day after bombs dropped on Pearl Harbor. "Every single man, woman and child is a partner in the most tremendous undertaking of our American history. The following abstracts, derived from three papers presented at the thirty-seventh annual meeting of the National Tuberculosis Association, indicate the important role played by the medical profession in the victory effort."

#### CIVILIAN HEALTH AS A FACTOR IN NATIONAL DEFENSE

(Miller, K. E. *Am Rev Tuberc* 44: 637-650, 1941)

The stem from which all manpower springs is the civilian population. The strength of the branch can be no greater than that of the stem. How strong is the stem? The findings of the National Health Survey made in 1935-36 afford some measure.

It may be estimated that 70,000,000 sick persons each year lose over one billion days from work or customary activities, and that the cost of illness and premature death in this country amounts annually to about \$10,000,000,000. The decline in the total death rate has been accomplished largely by lifesaving in infancy and childhood, which allows larger numbers to reach the age of maturity. Consequently, there is an upward trend in diseases of middle and old age, such as heart disease, nephritis, cancer and diabetes.

More than half of all tuberculosis deaths occur in the age group fifteen to forty-five. This heavy loss comes approximately within the age limits for military service. And for every death, there are approximately 10 clinical cases of illness from tuberculosis.

Disabling conditions among children, dental defects, venereal diseases, pneumonia, malaria and accidents are other leading causes of death and disability. The mental hospitals contain about 500,000 inmates, with 50,000 on parole, and about 75,000 patients are in institutions for the feeble-minded and epileptic.

Studies of the economic status of families shows a direct correlation of sickness with low income. Disability due to illness was nearly two and a half times as great among persons in the income group under \$1200 (an

nually) as in the group above \$3000. When it is recalled that the low-income groups constitute a large proportion of those who are employed in industries more or less directly connected with national defense, the losses sustained as a result of unnecessary illness may be regarded in the light of domestic sabotage.

#### PULMONARY TUBERCULOSIS, ITS EXCLUSION FROM THE NAVY

(Duncan, R. E. *Am. Rev. Tuberc.* 44:651-657, 1941)

Compactness of living spaces aboard a naval vessel is a necessity. Advances in ship construction from the standpoint of ventilation and sanitation in general have been made, but men living aboard are still somewhat crowded. Under such conditions, an open case of tuberculosis is a real menace. Medical officers are on the alert, but the average sailor likes to think of himself as rugged and hardy and will not, as a rule, report to the sick bay unless he really feels sick.

No applicant showing any degree of adult type tuberculosis is acceptable. Men in the service who develop tuberculosis are retired and are not subject to recall to active duty, even with long-standing arrest and minimal lesions.

The Medical Department of the Navy has recognized that at least 30 to 40 per cent of minimal cases will be missed by well-trained phthisiologists, depending on the conventional methods of physical examination alone. The criterion to be used in weeding out tuberculosis must be radiography. What form of radiography might be most practical for the Navy has been studied for some years. After the advantages and disadvantages of the several methods now available were considered, fluorography with the 35-mm. film was found to be the best solution to the problem.

Speed is an important factor during a period of mobilization. A smoothly working team can easily turn out from 100 to 150 films per hour. At present, examinations are not exceeding the rate of 80 per hour, in the interest of careful posturing and some regard for the life of the x-ray tube.

However, these miniature films are not used for fine diagnostic work, but serve merely as a sieve to screen out the abnormal from the normal chest. In any case showing a lesion or even a questionable area, a standard 14-by-17-inch celluloid film is made for confirmation and accurate diagnosis. The method has definitely passed the experimental stage, and it is ideal for mass thoracic-survey work. At one training station, photofluoroscopic examinations of 5171 recruits were made. These men had already passed two stringent physical examinations. Yet, of these recruits, 15 men showing soft infiltration in the lungs and 3 with multiple calcification and fibrosis of a disqualifying extent were transferred to the hospital for further study and disposition.

The incidence of tuberculosis in the Navy is not high during normal times and has been steadily declining.

#### TUBERCULOSIS IN THE ARMY

(Pollock, W. C. *Am. Rev. Tuberc.* 44:658-674, 1941)

This paper, presented May 8, 1941, was largely a criticism of certain faults in the program for detecting tuberculosis among inductees. By December, 1941, however, the author was able to add to the summary the following:

"Since presenting this paper, the Army Tuberculosis Survey has been improved. Practically all inductees are now being x-rayed prior to induction into the Army.

Tuberculous inductees are not enrolled. It is considered that the Army now has an excellent program of tuberculosis survey."

The mobilization survey of 1941-45 will be the greatest case-finding effort ever carried out in this country. Its purpose will be to detect chest diseases that would incapacitate the inductee for active military service; to detect diseases that may be so aggravated by military service that the inductee becomes incapacitated for military service; to detect, especially, pulmonary tuberculosis with subsequent isolation of the patient from contact with young noninfected persons; to report all tuberculous inductees to proper state health authorities.

The demobilization survey will consist of the routine general physical examination followed by an x-ray examination of the chest. Thus far, the x-ray examination has been made shortly after induction. and for this purpose the 14-by-17-inch film has been mostly used. At present and in the future, the x-ray survey will be made chiefly by use of fluorograms, with 4-by-5-inch film. Two films are made, one of which is sent to the War Department for permanent record. On demobilization two additional fluorographic films will be made, with like disposition of the films.

The chief fault of this plan, namely, that the x-ray film of the chest is usually not made until after induction has been corrected.

Another fault is that inductees may be discharged on their own care unless in need of hospitalization. Medical officers will tend to err on the side of safety and many tuberculous inductees will be sent to Army hospitals who should have been discharged to their homes. When viewed from the standpoint of epidemiology, however, this may have the advantage of bringing a large number of cases under control and thus decreasing tuberculosis in the community.

Mobilization regulations allow the induction of a person with reinfection tuberculosis when the process is minimal in extent and arrested. This can be done when, in the opinion of the examiner, the lesion is not likely to become reactivated under the conditions of military service. This is a dangerous exception, for many experts are able neither to estimate properly the true potentialities of a fibrous, tuberculous process nor the "condition of military service."

Through this contemplated survey, thousands of new cases will be detected. It is essential to plan for their care. No official estimate of the number that will be discovered has yet been made, but the author hazards the guess that between 1941 and 1945, a grand total of 88,000 cases will be detected.—Reprinted from *Tuberculosis Abstracts*, March, 1942.

#### NOTES

Dr. Arlie V. Bock, Henry K. Oliver Professor of Hygiene, and David B. Dill, director of the Fatigue Laboratory, Harvard University, have been chosen to deliver the James M. Anders Lecture before the College of Physicians of Philadelphia on April 1.

The School of Medicine of Middlesex University has recently announced that it has adopted the three-year accelerated educational program. The present school year will end on June 15, and the new school year (1942-1943) will start on July 1, instead of in September. Steadily rising costs of operation have necessitated the raising of the annual tuition fee to \$450.00, payable in three installments.

(Notices on page x)

# The New England Journal of Medicine

Copyright, 1942, by the Massachusetts Medical Society

VOLUME 226

APRIL 2, 1942

NUMBER 14

## OPTIMAL DOSAGE AND THE RECIPROCAL RELATION OF DESOXYCORTICOSTERONE ACETATE AND SODIUM IN ADDISON'S DISEASE\*

THOMAS H. MCGAVACK, M.D.†

NEW YORK CITY

**D**ESOXYCORTICOSTERONE is a readily available ketosteroid of the adrenal cortex and has greater life-maintaining qualities than any chemically pure constituent isolated to date.<sup>1-5</sup> Nevertheless, such extreme practical difficulties have been encountered in its clinical application in cases of Addison's disease<sup>6-9</sup> as to lead to its condemnation in certain quarters.<sup>6,9</sup>

The drug affords satisfactory replacement therapy for adrenocortical deficiency so far as the vital and sodium-regulating factors are concerned. Moreover, it enables the animal to store and use carbohydrate food and exogenous protein satisfactorily, but fails to restore the ability of the organism to produce sugar and glycogen from endogenous protein and fat. If properly used, it enables the patient with Addison's disease to resume his usual daily activities.

The dangers in the application of desoxycorticosterone have been centered around its predominant effect on electrolyte metabolism—with particular reference to sodium. The early failure to understand clearly the extent of this action has been responsible for the untoward reactions observed. Wholesale condemnation of the drug on this basis alone seems presumptuous, since very few useful additions to the therapeutic armamentarium of the physician have been without limitations.

It has been shown that sodium and desoxycorticosterone exert a similar beneficial action in the adrenalectomized animal, and that although salt in sufficient quantity in such animals maintains life, it does not afford the same vitality as a combination of the two agents.<sup>10,11</sup> The ability of desoxycorticosterone to prevent salt loss and to correct faulty potassium exchange in the subject with

adrenal insufficiency is its best known action. At the same time, it is the one that has led to most of the complications.

During the last two and a half years, 6 cases of Addison's disease have been treated with desoxycorticosterone acetate, together with regulation of the sodium and potassium intake. From observation on this group of patients, two conclusions concerning the efficacy and safety of desoxycorticosterone as a therapeutic agent can be drawn: the patient with Addison's disease can be satisfactorily maintained in good health by the judicious use of desoxycorticosterone acetate and the simultaneous regulation of sodium and potassium intake; and within certain limits, a reciprocal relation exists between the amount of sodium to be ingested and the dose of desoxycorticosterone acetate necessary to maintain the subject in good condition.

The criteria of "maintenance in good condition" include a sense of well-being on the part of the patient, a slow, steady gain in weight or a maintenance of normal weight once attained, a return of blood pressure to normal and its fixation there, a gradually rising cardiothoracic ratio,—not to be allowed to exceed 0.50, and preferably maintained around 0.46,—normal values for sodium and potassium in the blood serum and urine, and improvement toward normal in the configuration of glucose-tolerance curves.

The repeated determination of the blood sodium and potassium values and of the glucose-tolerance curve is comparatively difficult for the average practitioner and often barred by the expense entailed to the patient. Such determinations are not essential, so long as the other reasonably simple procedures are carried out. Rapidly rising cardiothoracic ratios should be avoided. This point warrants some emphasis. In no case have I seen hypertension or edema whose onset was not pre-

\*From the Department of Medicine, New York Medical College, and the Medical Service, Flower and Fifth Avenue Hospitals and Metropolitan Hospital.

†Associate professor of medicine, New York Physician, Flower and Fifth Avenue Hospitals and Metropolitan Hospital.

ratio between the transverse diameter of the heart and the transverse diameter of the chest. Since these patients almost invariably need a roentgenogram of the heart and lungs as a part of the initial diagnostic survey, subsequent changes can be compared to the size of the heart as obtained in this first study. If necessary, these changes may

signs of overdosage, in no case resulting seriously.

Using the criteria mentioned, it has been possible to bring about in these 6 patients with Addison's disease a state of stabilization sufficiently good to permit each to return to his previous walk in life. Particular care has been taken to regulate sodium intake and desoxycorticosterone dosage re-

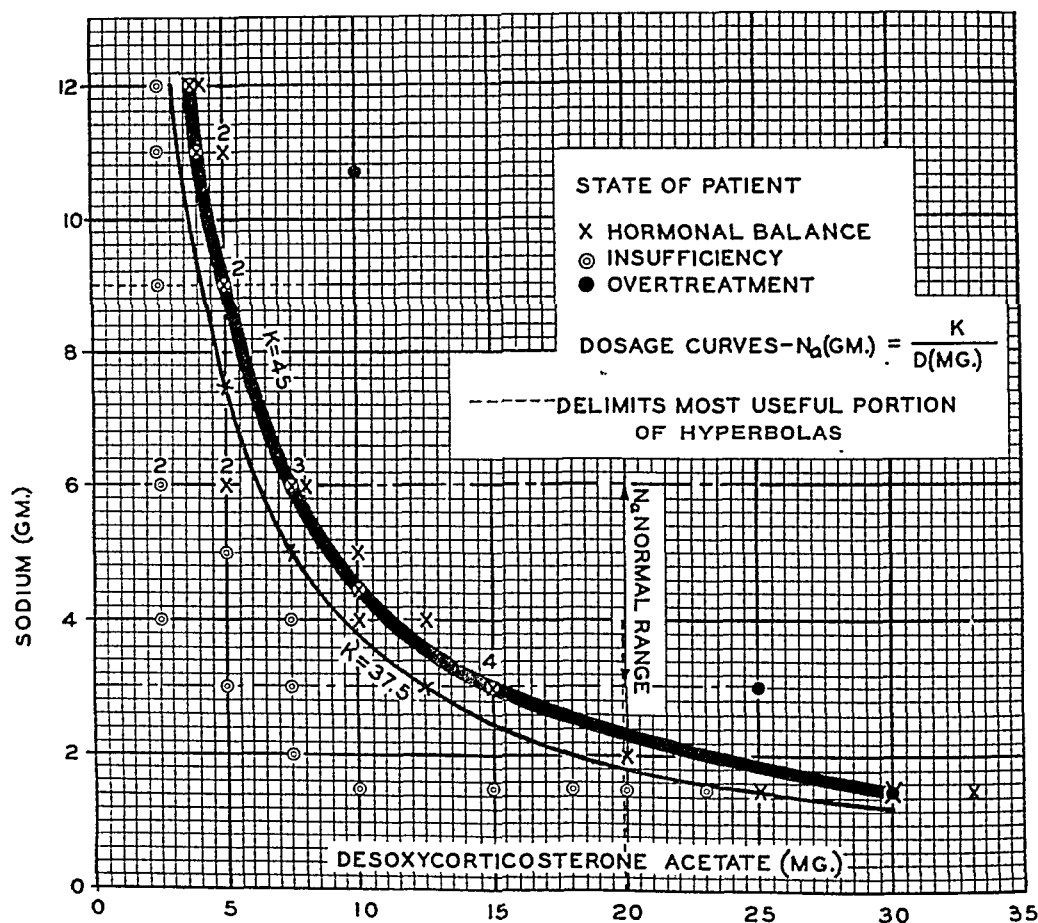


FIGURE 1. Clinical Results in 6 Cases of Addison's Disease following the Use of Forty-seven Different Ratios for the Daily Intake of Sodium and Desoxycorticosterone Acetate.

The numerals indicate the number of cases represented by a given point.

be charted in the office even less expensively by orthodiascopy.

Signs of overdosage with desoxycorticosterone acetate include a sudden gain in weight, hypertension, a cardi thoracic ratio above 0.50, edema of any part of the body (late manifestation) and a definite feeling of malaise not unlike that prior to the administration of any treatment for the disease. Indeed, in the early handling of patients by the use of desoxycorticosterone acetate, these symptoms were considered an aggravation of the state of adrenal insufficiency, and more of the drug was administered.<sup>9</sup> Manifestations may vary from patient to patient, but the extreme sense of fatigue and weakness that is so characteristic of the Addisonian state itself is common to all patients. On three occasions, I have observed

ciprocally, since failure to recognize the dangers of too much of one in relation to the other appears to have caused the difficulties seen in the management of the disease. To analyze the results, each change of sodium administered or desoxycorticosterone used has been charted in relation to the other, and the state of health of the patient carefully checked while on each such variation of his regime (Fig. 1).

The amount of sodium and desoxycorticosterone acetate given daily was recorded for each of the 47 trial periods. The patient remained on each of the changes made for not less than six weeks, except in those cases in which signs of overdosage became apparent, or in those in which signs of insufficiency were severe before such a period was completed. As judged by the criteria already mentioned, the

patients were in hormonal balance in 28 of the trial periods, in insufficiency in 16, and subject to complications in 3. If an attempt is made to pass a curve through a majority of the plotted points in which a balanced ratio between sodium and desoxycorticosterone exists, the pattern of such a curve clearly becomes that of a hyperbola,  $Na = k \div D$ , where  $Na$  represents the daily intake of sodium in grams,  $D$  the daily dose of desoxycorticosterone acetate in milligrams, and  $k$  the constant. When substitutions were made in this formula from figures used in ascertaining the optimum dosage in a number of cases,  $k$  equaled 45 in 14 periods and 37.5 in 4, and in the remaining 10 periods, lay between 30 and 37.5 in 2, between 37.5 and 45 in 2, and between 45 and 55 in 6. In other words, a hyperbola with the formula,  $Na$  (gm.)  $= 45 \div D$  (mg.), passes through 14 of 28, or 50 per cent, of all the trials during which the patient was shown to be in a satisfactory state of balance; the next greatest frequency is given by the formula,  $Na$  (gm.)  $= 37.5 \div D$  (mg.), which passes through 4 of 28, or 14 per cent, of the points of optimal dosage plotted. No complications arose when ratios lay close to those indicated by either of these curves or by points between them. The area between them might be spoken of as the "zone of safety" for the selected dosage of sodium and desoxycorticosterone acetate. My experience suggests that dosages should lie closer to the first-mentioned curve with a constant of 45 (heavier line). It seems obvious, however, that no predetermined ratio for sodium and potassium is satisfactory in all cases, since the degree of adrenal insufficiency varies from patient to patient. Nevertheless, from present evidence, this variation takes place over a rather narrow range of equivalents, in contrast, for example, to the wide variation of insulin dosage necessary in the treatment of patients with diabetes mellitus. Such a difference can possibly be explained on the basis that thus far it has been impossible to produce "grades" of adrenal insufficiency experimentally. The operator either removes so much of the gland that the animal dies, or by leaving even the slightest fraction more, enables the animal to survive, apparently in the best of health.

As with any other biologic relation capable of expression in a hyperbolic curve, limits of applicability are in evidence. My observations suggest that patients do best when the daily intake of sodium is varied between 2.3 and 9.0 gm., and that of desoxycorticosterone acetate from 5 to 20 mg. (Fig. 1). Patients on a higher quantum of sodium with concomitantly less desoxycorticosterone had less endurance and, in general, felt "less fit" than when the ratios noted above were observed. Moreover, higher dosages of desoxycorticosterone

were associated with more nearly normal glucose-tolerance curves,<sup>12</sup> although carbohydrate metabolism could not be regarded as completely normal in any case. The highest doses of desoxycorticosterone acetate—20 to 33 mg.—have been quite satisfactory from the patients' point of view. The majority state that they "feel fine." Despite the concomitantly low salt intake, however, blood pressures tend to remain at upper normal levels, and it has been suggested that some storage of sodium, with possible "packing" of the cells, may be taking place.<sup>13,14</sup> It seems logical and practical to make the range of dosage of desoxycorticosterone conform to the normal range of sodium intake (3 to 6 gm.) as indicated by the interrupted line in Figure 1. If this is done, it appears that from 7.5 to 15.0 mg. of desoxycorticosterone acetate can be given daily over relatively long periods. I had originally gained the impression that such a dose was too high for continued use without careful supervision of the patient; this may yet be proved true, for it is quite possible for some regeneration of cortical tissue to take place, or for aberrant tissue to initiate functional activity. If the curve of the lower constant (37.5) is used, this dosage in the range mentioned lies between 6.3 and 12.5 mg. daily. I consider this a perfectly safe amount in any patient with proved Addison's disease.

Previously stabilized patients in whom the product of sodium in grams and desoxycorticosterone in milligrams was changed to 15 or less (6 trials) quickly developed obvious signs of adrenal insufficiency, with a loss of weight, a fall in blood pressure, cardiothoracic ratio and blood serum sodium, and a return of progressive weakness. Such low values should be completely avoided when one plans the therapeutic regime of the patient with Addison's disease.

Three patients showed signs of toxicity from overtreatment. Two of these are as follows:

CASE 1. H. L. had been receiving 10.7 gm. of sodium and 10 mg. of desoxycorticosterone acetate daily for 9 days, when she developed swelling of the ankles, puffiness about the eyes, slight dyspnea and increased weakness. There was no pulmonary edema, but the heart was markedly enlarged, with a cardiothoracic ratio of 0.58, a heart volume of 693.0 cc. per square meter of body surface, and a blood volume of 5963 cc. (theoretic normal, 4466 cc.). Sixteen days previously, these values had been 0.41, 328.8 cc. and 3507 cc., respectively. This patient was later given 15 mg. of desoxycorticosterone acetate daily when the sodium intake was limited to 3 gm. For 6 months, there were no untoward effects. It is obvious, therefore, that the toxic reaction was not a factor of the drug alone, but was produced by the interaction of the steroid with available sodium.

CASE 2. J. P., a 60-year-old man, was in an extremely emaciated condition, bordering on crisis, when first coming under treatment. For 6 months, he had suffered from a continuous diarrhea, with severe, intermittent,



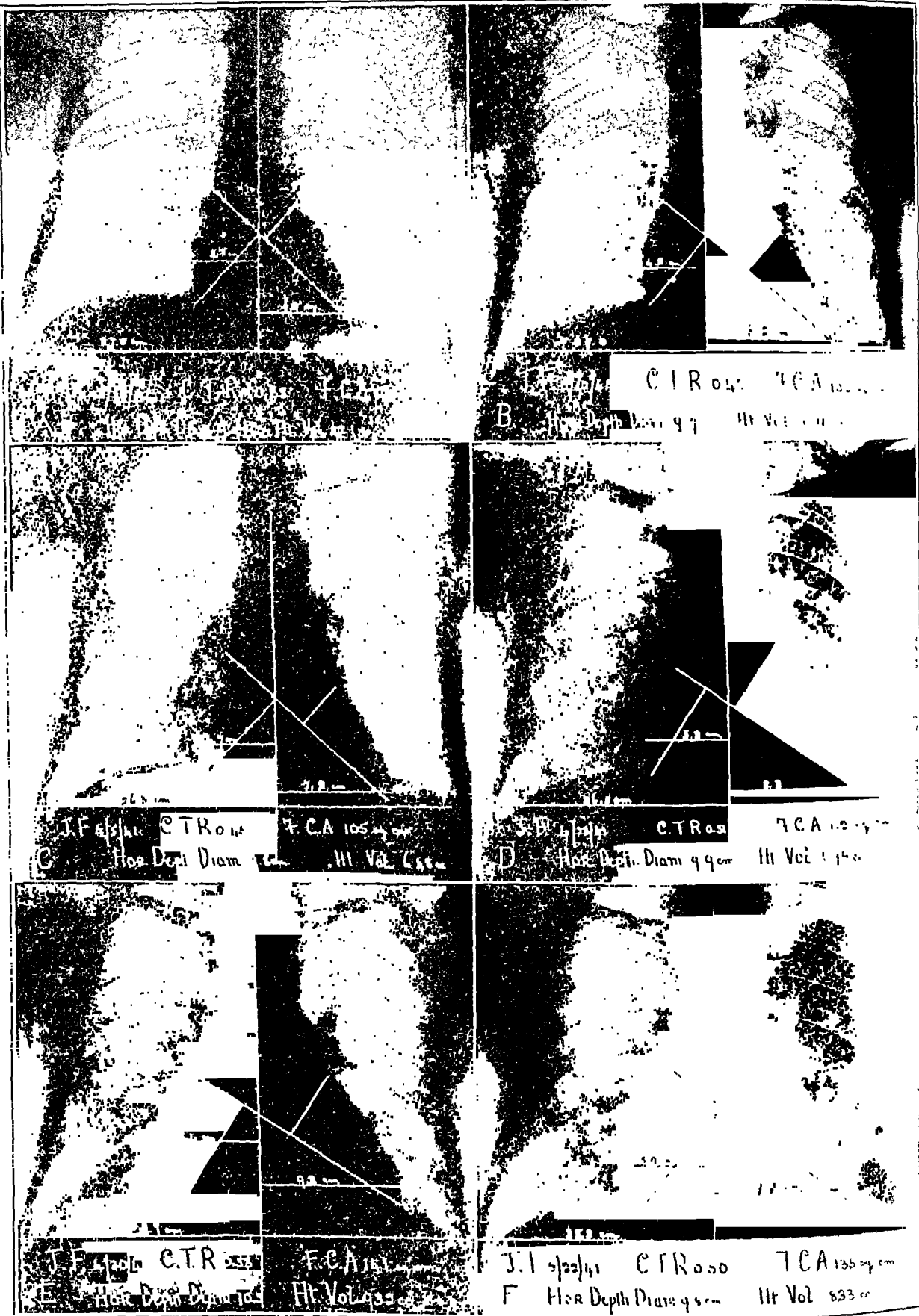


FIGURE 2. Serial Variations in Teleroentgenographic Shadows in Case 2 while the Patient was on a Constant Intake of Sodium and a Changing Dosage of Desoxycorticosterone Acetate.

crampy, upper abdominal pain. Throughout treatment, he was maintained on a daily dosage of 3 gm. of sodium. It was necessary to give him 25 mg. of desoxycorticosterone acetate daily before the abdominal symptoms were completely controlled, although he had shown improvement in his general condition when the amount of steroid was 15 mg. He showed no signs of toxicity from 25 mg daily until the end of 2½ weeks, when the blood pressure was 148/84 (normal for 60 years of age) and other factors, such as a sense of well-being, weight and serum electrolytes, were within normal limits, but the cardiothoracic ratio had increased from 0.45 to 0.51 (Fig. 2 and Table 1).

One week after changing to 1.5 gm. of sodium and 30 mg. of desoxycorticosterone acetate daily, the patient developed mild occipital headaches and slight ankle edema. The weight, blood pressure and cardiothoracic ratio, which had previously been 58.6 kg, 140/72 and 0.42, respectively, became 59.0 kg., 164/120 and 0.48, respectively. Subjectively, the only symptom was headache, which never required medication. Within a week, the edema subsided, the headaches disappeared, and the blood pressure returned to within normal limits (138/85). The patient was maintained on the same regime for an additional 3 weeks, and continued to gain in weight and strength. The cardio-

TABLE 1. *Changes in Cardiothoracic Ratio in Case 2.*

X-RAY FILM (FIG. 2)	DATE	CARDIO-THORACIC RATIO	BLOOD PRESSURE mm Hg.	DESOXYCORTICOSTERONE ACETATE mg.	COMMENT
A	1/23/41	0.38	70/50	0	Cortical insufficiency
B	3/12/41	0.45	95/65	5 (1 week) 10 (2 weeks)	
C	4/5/41	0.45	100/70	20 (2 weeks)	Good clinical condition
D	4/23/41	0.51	116/72	25 (2½ weeks)	"Feels fine," and gaining rapidly, note high cardiothoracic ratio, sodium desoxycorticosterone product high at 75
E	4/30/41	0.53	148/84	25 (1 week)	Went into cardiac failure on this date; note the normal blood pressure but high cardiothoracic ratio
F	5/22/41	0.50	132/80	15 (3 weeks)	Lung fields clearing, cardiothoracic ratio decreasing, sodium desoxycorticosterone product normal at 45.

In spite of the rise of the ratio above 0.50, it was decided to continue the previous regime, to complete special studies reported elsewhere.<sup>12</sup> One week later, the blood pressure had risen to 148/84, the cardiothoracic ratio to 0.53, and the patient suddenly developed ankle and pulmonary edema, breathlessness, dilatation of the heart and weakness.

The second case demonstrates the fact that the cardiothoracic ratio is one of the earliest and most sensitive indicators of overdosage. I still believe that ratios should be maintained in the neighborhood of 0.46,<sup>15</sup> to avoid any possible danger of toxic manifestations, although outspoken symptoms have not been seen with any ratios below 0.51. This is the only case in which frank cardiac failure occurred. Such a disturbance appeared only after three and a half weeks on a drug and sodium ratio nearly twice that which would have been indicated by the "dosage curves" of Figure 1. This certainly suggests that the drug can be used without danger in the average case, if proper attention is paid to simple rules of administration.

The third reaction observed, which was a most interesting and yet a very mild one, disappeared without any change in treatment.

CASE 3. E. M., a 24-year-old man, for over a year was comfortably stabilized on a daily sodium intake of 6 gm. and a sufficient number of pellets by implantation to yield 25 mg. of hormone daily.\*

\*By trial-and error removals and weighings in this and 3 other cases, it was estimated that each 150 mg. pellet of desoxycorticosterone acetate from the source available (Schering Corporation) gives a daily absorption of 1 mg. Each milligram so absorbed appears to equal 3 mg. of material when injected in oily suspension. It is essential to know the source of pellets for implantation, since the shapes, sizes and hardness alter the rate of absorption and vary considerably with different manufacturers.

thoracic ratio was stabilized at 0.46, the serum sodium remained within normal limits, and, moreover, the absorption and utilization of glucose, as indicated by the oral glucose-tolerance curves, improved materially.

This is the only case in which a reaction occurred when the product of the daily ration of sodium in grams and desoxycorticosterone acetate in milligrams was 45 or less. The fact that the reaction disappeared spontaneously is not explained. It has been suggested that with such high doses of hormone—despite the concomitantly very low ingestion of salt—a packing of sodium into the interstitial spaces and into the cells themselves must occur.<sup>13, 14</sup> It therefore seems unwise in the present state of knowledge to utilize the proportions suggested by the extreme right end of the hyperbolic curve for very long periods.

#### SUMMARY

Forty-seven variations in the ratios of sodium and desoxycorticosterone acetate used in the management of 6 patients with Addison's disease were plotted with respect to each other.

In 28 trial periods, the patient was in hormonal balance, that is, in good clinical condition with normal values for weight, blood pressure, cardiothoracic ratio and serum electrolytes. In 3, there were signs of toxicity from overdosage, and in the remaining 17 there was clinical and laboratory evidence of adrenal insufficiency.

All the ratios representing patients in "good clinical condition" have been shown to lie on, near or between the portions of two hyperbolic curves, whose constants are 37.5 and 45 respec-

tively. Fourteen actually lay on the latter curve. The area between these curves may be spoken of as the "zone of safe dosage."

As a general rule, patients felt best and showed most nearly normal carbohydrate utilization on dosages of hormone ranging between 10 and 20 mg. daily, with corresponding values for sodium, whereas larger doses did not augment these effects materially. Patients receiving less than 5 mg. of hormone daily, and concomitantly more than 9 mg. of sodium daily, did not "feel fit," despite the maintenance of weight, blood pressure and serum electrolytes within a normal range of values.

### CONCLUSION

Patients with Addison's disease can be safely and satisfactorily treated with desoxycorticosterone acetate, provided that attention is paid not only to the usual criteria of well-being, but also to the regulation of the dosage of drug and intake of sodium in a reciprocal manner. Values for these two variables represented by points lying on or between portions of hyperbolic curves in which the constants are 37.5 and 45, respectively, have been found to yield satisfactory results in clinical cases of insufficiency of the adrenal cortex.

1 East 105th Street

### REFERENCES

1. Wells, B. B., and Kendall, E. C. The influence of the adrenal cortex in phlorhizin diabetes. *Proc. Staff Meet., Mayo Clin.* 15:565-573, 1940.
2. Ingle, D. J. The effect of two cortin-like compounds upon the body weight and work performance of adrenalectomized rats. *Endocrinology* 27:297-304, 1940.
3. Gordon, E. S. The use of desoxycorticosterone and its esters in the treatment of Addison's disease. *J. A. M. A.* 114:2549-2551, 1940.
4. Sevringhaus, E. L. Desoxycorticosterone acetate in Addison's disease. Reese, Lewis and Sevringhaus's *Yearbook of Neurology, Psychiatry and Endocrinology*. 856 pp. Chicago: Year Book Publishers, 1940. P. 703.
5. Ingle, D. J., and Thorn, G. W. A comparison of the effects of 11-desoxycorticosterone acetate and 17-hydroxy-11-dehydrocorticosterone in partially depancreatized rats. *Am. J. Physiol.* 132:670-678, 1941.
6. Ferrebee, J. W., Ragan, C., Atchley, D. W., and Loeb, R. F. Desoxycorticosterone esters: certain effects in the treatment of Addison's disease. *J. A. M. A.* 113:1725-1731, 1939.
7. Wilder, R. M. Progress in treatment of Addison's disease. *Proc. Staff Meet., Mayo Clin.* 15:273-277, 1940.
8. Kuhlmann, D., Ragan, C., Ferrebee, J. W., Atchley, D. W., and Loeb, R. F. Toxic effects of desoxycorticosterone esters in dogs. *Science* 90:496, 1939.
9. McCullagh, E. P., and Ryan, E. J. Use of desoxycorticosterone acetate in Addison's disease. *J. A. M. A.* 114:687, 1940.
10. Anderson, E., Herring, V., and Joseph, M. Salt after adrenalectomy: carbohydrate stores in adrenalectomized rats given various levels of sodium chloride. *Proc. Soc. Exper. Biol. & Med.* 45:488-493, 1940.
11. Anderson, E., and Herring, V. Effect of NaCl and desoxycorticosterone on body weight and carbohydrate stores of adrenalectomized rats. *Proc. Soc. Exper. Biol. & Med.* 43:363-366, 1940.
12. McGavack, T. H., Charlton, G. P., and Klotz, S. The effect of desoxycorticosterone acetate on glucose tolerance in normal individuals and in patients with Addison's disease. *J. Clin. Endocrinol.* 1:824-830, 1941.
13. Miller, H. C., and Darrow, D. C. Relation of serum and muscle electrolyte, particularly potassium, to voluntary exercise. *Am. J. Physiol.* 132:801-809, 1941.
14. Thorn, G. W. Personal communication.
15. McGavack, T. H. Changes in heart volume in Addison's disease and their significance. *Am. Heart J.* 21:1-16, 1941.

## AN IMPORTANT ETIOLOGIC FACTOR IN SO-CALLED "FOOT STRAIN"\*

ROBERT B. OSGOOD, M.D.†

BOSTON

ROBERT Louis Stevenson once said that after the old man has listened to the young man, the old man usually remarks, "Well, my boy, I thought that at your age." We older men will do well if we constantly remember Stevenson's comment to the effect that the old man's remark suggests that "the young man was probably right." Nevertheless, if as we grow older we can manage to keep a reasonably open mind and do not ride our hobbyhorses too hard, experience may be the worthy teacher that it is proverbially said to be. Consequently, I have the temerity to call attention to what I believe to be an important and somewhat neglected etiologic factor in foot strain or, as the condition is still erroneously called, "flat foot." The subject is hackneyed, but the sufferers from foot strain are still many.

May I refresh your minds as to the essential rudimentary anatomy of bipedal symptomless weight bearing?

Good posture, which conforms to the lines of gravity, will be taken for granted. The normal lines of weight bearing, transmitted as they are

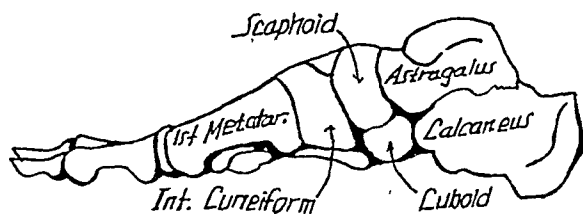


FIGURE 1. Medial Aspect of the Bones of the Foot.

through the tibias, fall considerably to the inner or medial sides of the feet. So far as the bony anatomy of the lower leg and foot is concerned,

\*Read at the annual meeting of the New England Surgical Society, Hanover, New Hampshire, September 6, 1941.

†John Ball and Buckminster Brown Professor of Orthopaedic Surgery Emeritus, Harvard Medical School.

the lines of weight bearing tend to depress the feet on their medial aspects. What resists this straining force? Neither of the two bony arches of the foot—the longitudinal arch from the os

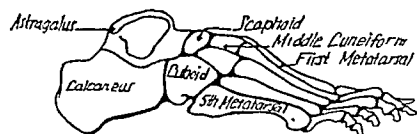


FIGURE 2. Lateral Aspect of the Bones of the Foot

calcis to the metatarsal heads and the anterior transverse arch formed by the heads of the metatarsal bones—has any keystone worthy of the name (Figs. 1 and 2). One, therefore, cannot depend on the bony configuration to resist this deforming, inward, sagging force. The weight is transmitted through the tibia to the astragalus at the ankle joint, and thence to the os calcis and the ground. The main joint between the astragalus and the os calcis is a shallow ball-and-socket joint, but the projection of the sustentaculum tali on the inner side of the os calcis offers a prop that would keep the astragalus from rolling medially or inwardly, provided the os calcis could retain the vertical plane. The os calcis is held in this vertical plane by the strong posterior calcaneo-scapoid and the tibioastragaloid or deltoid ligaments, the plantar ligaments and the capsules of the joints of the tarsal bones (Fig. 3). These

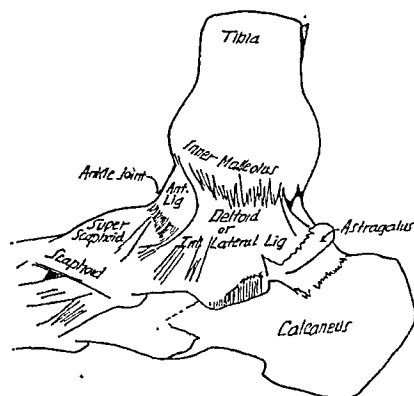


FIGURE 3. Ligaments Supporting the Os Calcis.

ligamentous structures are only passive supports and will stretch and weaken if a continuous force such as faulty weight bearing is active

By far the major factors that maintain proper weight-bearing lines in the feet are the muscles of the lower leg, which have their insertions in the feet, and to a lesser extent, the intrinsic muscles of the feet themselves. These are active, not passive, supports.

Duchenne<sup>1</sup> (1806-1875), that brilliant son of a Boulogne sea captain, invented an electric apparatus that determined the exact function and comparative strength of the muscles by stimulating their contraction. It had previously been necessary to make skin incisions and to stimulate the muscles by actual contact. His invention of moist electrodes over the muscle bellies did away with

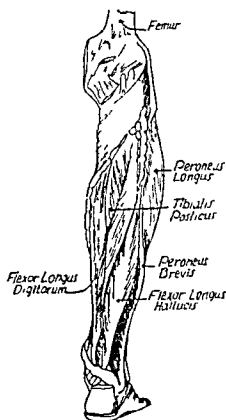


FIGURE 4. Posterior View of the Muscles of the Lower Leg.

the necessity for surgery and enormously simplified the study of muscle function. One of the many increments of knowledge that this careful pioneer added came from his study of the muscles of the lower extremities in relation to weight bearing. He reached the conclusion that faulty weight bearing and foot strain were most commonly caused by a faulty balance between the group of muscles that inverted the foot and elevated the arches and the group whose contraction tended to evert the foot and depress the arches. His conclusion was sound, but few seem to have applied it to the relief of foot strain.

Figures 4 and 5 illustrate the principal muscles of these two synergistic but more or less antagonistic groups. The first group may be called the inverters or the maintainers of symptomless weight bearing; if the second—the everters—overbalances the inverters, foot strain usually results.

Many years ago, I was interested in several patients who consulted me because they had been rejected for the fire and police departments of "flat feet." They protested

had any symptoms from their pedal extremities, and a few of them boasted of their prowess as long-distance walkers and of the prizes they had

inverters or adductors and the everters or abductors. A simple and fairly foolproof apparatus was devised, which is illustrated by Figure 6.

The late Dr. Arthur T. Legg was then in charge of the large foot clinic at the Carney Hospital, and I was working in the equally large clinic of the Massachusetts General Hospital. Dr. Legg, always the kindest of men, did the testing at the Carney Hospital. We agreed to test the comparative strength of these two groups of muscles in four different types of feet: symptomless feet, which exhibited, in shoe wear, and in walking, normal weight-bearing lines; feet that were symptomless but in which a slight sag toward the inner side (what is usually called pronation) was exhibited; feet that tired easily and were usually tender to pressure beneath the calcaneoscaphoid ligaments and frequently exhibited calluses beneath the anterior arches—this group showed still more faulty lines of weight bearing than those of the second type, that is, more exaggerated pronation; and painful feet, usually but by no means always flat, which were tender to plantar pressure and flexible to passive motion, and were covered by shoes that bulged on their inner sides—these are commonly called “acute flat feet,” and their possessors seem to have lost the joy of life.

Dr. Legg and I agreed not to discuss or compare our findings until we had tested a sufficient number of feet to give some reliability to our statistics. When a total of a hundred and twenty tests had been made, including all the four classifications, we compared our figures. To our surprise and satisfaction, we discovered that the aver-

won in track sports. When they stood, their feet were certainly flat, but when they walked or ran their weight-bearing lines were perfect. Apparently, the fire and police departments had rejected

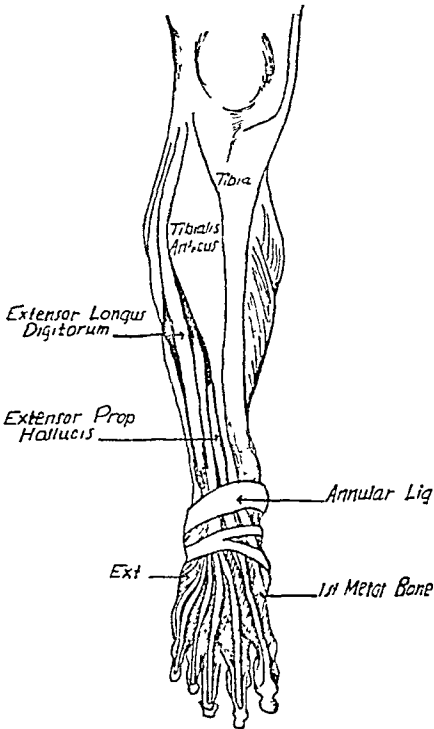


FIGURE 5. Anterior View of the Muscles of the Lower Leg.

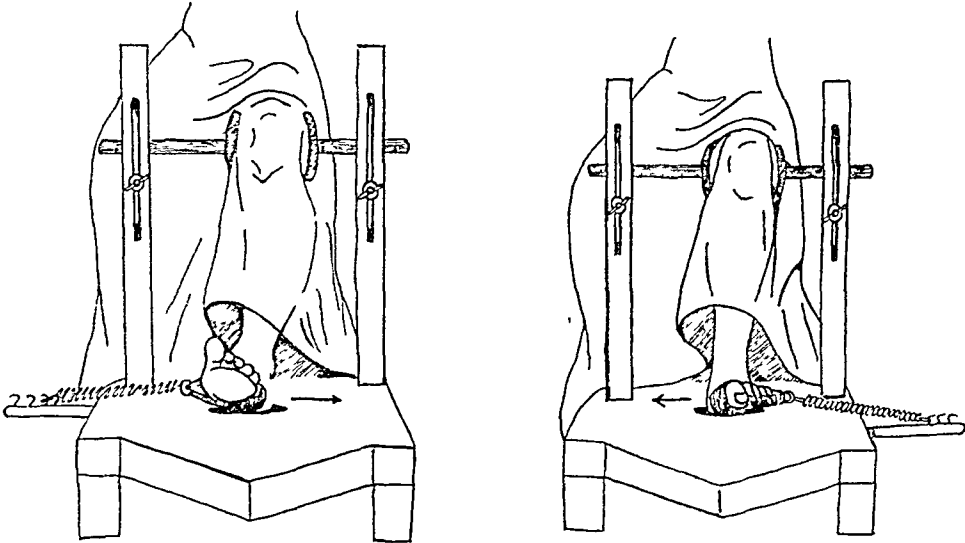


FIGURE 6. Apparatus for Testing the Strength of the Adductors and Abductors of the Foot.

excellent men because when they stood their feet were flat. I determined, therefore, in 1907, to make a study of the comparative strength in pounds pull of the two antagonistic groups of the

ages that we had independently computed in the two different clinics were well-nigh identical. The exact fractional percentages of the different groups were published in 1908.<sup>2</sup>

In the first group, which one may call the symptomless normal feet, the inverters of the foot, acting as protectors of the arches, were stronger than the everters or depressors of the arches in the ratio of approximately 5 pounds pull of the inverting protectors to 4 pounds pull of the everting depressors.

In the second group, also symptomless but exhibiting slight pronation, the pull of the two groups of muscles was approximately equal, but slightly in favor of the everters or depressors of the arches.

In the third group, that of patients with more pronated feet seeking advice because of symptoms of foot strain, the pounds pull of the everters or depressors of the arches was definitely stronger than that of the inverters or protectors of the arches.

In the fourth group, comprising the "acute flat feet," the ratio of the pounds pull of the inverters to that of the everters was approximately 4:5; in other words, the reverse of the ratio that existed in the test of normal symptomless feet.

On the basis of these tests, it seemed worth while to determine in some impartial manner the possible preventive and therapeutic implications of the findings. An opportunity to examine by means of these muscle tests the feet of probationer nurses was afforded by the superintendent of the School of Nurses at the Massachusetts General Hospital. These young women were taking up an occupation that required longer hours of standing and walking on harder surfaces than the majority of them had experienced. I was informed that in the rather large classes of probationers there had previously been a rough average of one nurse a week obliged to be off duty because of foot strain. For a year, I was allowed to examine and test in the manner I have described the feet of all the probationers soon after they took up their new duties, and to advise them in accordance with the findings of the test. If my memory is honest, no nurse who had followed the advice given on the basis of the test was laid up for foot strain during the year. Moreover, only one of the probationers who exhibited a normal balance test at her original examination reported for foot strain, and her condition proved later to be arthritic and not static. This seemed a little too good to be true, and I asked my colleague, Dr. Lloyd T. Brown, to repeat the clinical experiment the following year. He had the same good luck. The result had been economical for the hospital.

It seemed worth while to attempt to gain an impression of the incidence of faulty muscle balance in otherwise healthy young people. Through the

kindness of Miss Amy Homans, then professor of physical culture at Wellesley College, and Miss Randall, her assistant, the foot balance of 350 students was tested in the manner described. Faulty balances were found to be three times commoner than normal balances. Incidentally, Miss Randall reported that only a surprisingly small number of college girls were able to take walks of any considerable distance without general and foot fatigue. This was in 1912-1913, and it is to be hoped that the increase in athletics and the more sensible shoes have by now lessened the prevalence of foot strain in the female college students.

If, in the routine examination of a patient with a tired back and weary feet, one finds an abnormal wear of the shoes, indicating pronation, tenderness to pressure over the strained ligaments of the arches, the other classic signs of foot strain and a faulty muscle balance, what should be done? The first thing, in my opinion, is to make the patient understand what these findings mean in terms of his symptoms and the reasons why the measures proposed may be expected to relieve the symptoms that have induced him to seek advice. In my experience, this is time well spent.

As the first measure, one should recommend that shoes be designed on proper lines and of proper fit. One is inclined to inveigh against the modern ready-made shoe. It is true that the vagaries of fashion are responsible for many foot ills (especially the high heels with a small base), but one should pay a tribute to the manufacturers of shoes and the retailers of their products for their remarkable accomplishments. It is possible, except in the presence of fixed deformities, especially of the toes, to find for almost any shape of foot a ready made shoe that is both nondeforming and comfortable to wear. The detailed and extensive scientific work of Dr. R. Plato Schwartz,<sup>3</sup> professor of orthopedic surgery at the University of Rochester (New York), is worthy of unstinted praise in this connection, as are Professor Arthur Steindler's<sup>4</sup> excellent studies of the pathology of locomotion. The details of the mechanisms of the human gait are being accurately analyzed for the first time.

One should also correct or compensate for any departure from good weight-bearing lines that may be caused by improper body posture.

Moreover, one should make sure that there is no accessory inhibition, such as the lack of flexibility of the foot that is present when the power of dorsiflexion with the knee fully extended is less than a right angle because of contracted calf groups.

Finally, by some means, the normal muscle balance between the inverters or protectors of the

arches and the everters or depressors of the arches should be restored.

Other potential causes of foot strain should not be overlooked because of this emphasis on what I believe to be a neglected and remediable common cause. Fatigue, poor muscle tone after illness, unreasonably long hours of standing or walking on unreasonably hard surfaces, and vicious shoeing may be important etiologic factors. Overweight is often blamed, but in my experience the muscles usually develop in consonance with the gradual addition of weight if activity is maintained. The association of overweight, a sedentary life and foot strain was known in Biblical times, for in *II Samuel* (IX:13), we read, "So Mephibosheth dwelt in Jerusalem: for he did eat continually at the king's table; and was lame on both his feet."

How can a faulty muscle balance be changed into a normal one? "Aye there's the rub," for it entails exercises persistently followed and precisely performed. Most patients still expect a pill to cure their ills; almost as many pin their faith to an injection. A small number are willing to be massaged and exercised if the physical therapist does most of the work. Work on the patients' part is considered a personal virtue, although the reward of this virtue is their own betterment. If the explanation of the causes of their discomfort has been clear and convincing, I have found it possible to gain excellent co-operation from the vast majority of patients. The methods employed are those of dogmatism, cajolery and fear—not very idealistic methods, I admit, but productive of results.

I insist that patients take only one exercise, which is illustrated by the physician at the time of the visit. They are then presented with a carefully typewritten description of the exercise and four attractively colored marbles. The law of gradual increase in exercise is dogmatically laid down.

The patients are told that they must do these exercises between bed and breakfast, because muscles increase in strength only when they are rested before being exercised and have a chance to rest after being exercised. I remind them that the old adage still holds, "It is no use to whip tired horses," that although it is easier to do stupid exercises just before going to bed, it takes more "guts" when they are sleepy in the morning; if they go to bed without doing the exercises and get up that much earlier in the morning, their total sleeping time is no less and their muscular benefit much greater.

I inculcate fear by telling them that at the next visit—in two or three weeks—I shall be able to tell by the balance test whether or not they

have followed the instructions given. It has surprised me much to find how valuable an incentive to struggle such a fear of discovery of not having played the game often is.

The ready-made artificial foot supports commonly known as "foot plates" or "arch supporters," which stores and druggists carry, are, by and large, as much an abomination as one would expect a ready-made set of artificial teeth to be; but if intelligently fitted, such supports are often pain relievers, without having, as a rule, any curative value. I try to distribute the weight appropriately to the individual foot that needs a temporary support by making plaster casts, which are subsequently shaped to attain the desired end and from which light spring-steel or sponge-rubber supports are fashioned. I almost never make heavy or rigid foot supports, which tend to atrophy the intrinsic foot muscles. The type that is recommended for all but the rigid or very heavy or indolent patients provides a light springy support, which relieves the symptoms and holds the arches in position while the patients are attaining and learning how to maintain a normal muscle balance. Once this has been achieved and persevered in, artificial supports become unnecessary, and on any reasonably soft surface, weight bearing becomes a joy. One may even whisper the word "cure."

There have been very few disciples of this method of examination and therapy, although I have continued to employ it for over thirty years and still believe in its soundness. The fact that it is rarely used suggests very strongly that it is of little value, and yet I am somewhat comforted by the remembrance that Thomas's ring-hip splint remained almost unknown or at least unused except by him and a few colleagues for fifty years. But when his nephew, Sir Robert Jones, persuaded Sir Henry Gray, chief surgeon of the Third British Army, to order it applied to all the compound fractures of the thigh on the field before transportation to base hospitals, the mortality from this very common injury dropped from over 80 to 15 per cent. The Medical Department of the United States Army learned how to use this splint before casualties began, and it was the routine treatment prescribed throughout the course of the American Expeditionary Force. It proved an equal lifesaver for our soldiers. Today, all good ambulances are equipped with this almost forgotten splint or its modifications. "Splint 'em where they lie" is still a good slogan. It may be gathered that I think "Balance 'em where they stand" is another. Here is no thought of saving life but of enabling certain people to tread their measures with greater happiness and more comfort.

372 Marlborough Street

## REFERENCES

- 1 D'Jenne G F A *Physiologie des membres de l'homme et de l'animal* 2<sup>e</sup> ed. de l'expert médical électrique et de l'expert clinique et applicable à l'étude des paralysies et des déformations 821 pp Paris J B Baillière & Sons 186
- 2 Osgood R B The comparative analysis of the plantar and alar groups in the foot *Am J Orthoped Surg* 5:294-303 1908
- 3 Schwartz R P and Heil A L Some factors which influence the balance of the foot in walking *J Bone & Joint Surg* 19:131-44 1937
- 4 Scudler A *Mechanics of Normal and Pathological Locomotion in Man* 474 pp Springfield Clarendon Press 1935

## DISCUSSION

DR FRANK R OBER (Boston) Dr Osgood has demonstrated a very simple and excellent method for testing the basic difficulty in foot strain—that is, muscular weakness. I agree with him that the term flat foot is a bad one. The average person who has a flat foot hardly ever has any trouble with his foot, because the shoe that is bought in the market fits a flat foot and no other foot, therefore, this person is always protected.

Painful symptoms may occur in any type of foot—a flat foot, a highly arched foot or a moderately arched foot. The highly arched foot is the one that gives the most difficulty, however.

The patient should be examined sitting as well as standing. No satisfactory examination of the feet can be made in the standing position alone. A patient may pronate in the standing position and be labeled with a diagnosis of flat foot, whereas, when the foot is examined in the sitting position, the arch may be much higher. This type of foot is not a flat foot. The feet flatten out on standing because the patient has short posterior calf muscles, and to get the heel down on the floor, the front of the foot must go somewhere and usually goes into the abducted position, causing the ankle to roll inward. If the patient is asked to stand on tiptoe, it will be noticed that his arch is restored to the normal position. However, if a patient has worn flat shoes for years, the medial ligaments become stretched out, so that it is impossible for the patient to support his foot in the normal position, even with the assistance of the muscles.

There have been various attempts to legislate the heights of heels. One may as well try to legislate window glass for spectacles, because no two feet are alike.

According to a certain insurance company, growing pains

in children are due to rheumatism. The fact of the matter is that 999 out of 1000 cases are due to foot strain. The patient with a strong foot can wear any type of shoe, but if this patient is sick in bed for two or three months or has some debilitating disease even his foot will go to pieces when weight is put on it. Patients with short heel cords are much better off with a shoe that has a heel high enough to compensate for the loss of dorsiflexion.

Exercises should be simplified as much as possible since most people object to doing many. One exercise that uses practically all the muscles of the foot is much more satisfactory. In this exercise the patient is asked to curl his toes downward and at the same time to invert and dorsiflex his foot. This exercise affects the plantar muscles of the foot, the toe flexors and the anterior and posterior tibial muscles, all of which are the main support of the arch.

The main trouble with the whole shoe situation is that shoes are manufactured on a mass production basis. Since no two feet are alike in a single person it is out of the question to expect such a shoe to fit all types of feet. However, if a shank could be made to go into the shoe that could be adjusted to fit the foot, this problem would be solved.

The foot muscle testing apparatus that Dr Osgood has discussed is a simple device, not only in checking the weakness in foot muscles but also in checking, from time to time how well and how faithfully the exercises are being carried out.

DR OSGOOD (closing) I agree with everything Dr Ober has said, but the object I have been trying to emphasize is to get rid of the necessity of artificial supports. I am convinced that it is possible to do so in a great many cases. One method of doing it is to test the protectors against the depressors and then, if the balance is wrong and the depressors are stronger, as they very often are, and if the patient co-operates the strength of the protectors can be built up to a normal muscular mechanism is attained.

It is rather good fun to be able to wear sneakers once in a while, and it is still a pleasure to play tennis. One cannot do that without normal muscle protection.

After what Dr Ober has said about ready made shoes I think I should say something in defense of the shoe manufacturer, because it is remarkable that so few of us have to have our shoes made for us. If we select carefully, most of us can find a shoe that fits reasonably well and, with a normal balance, can escape foot strain.



## TOXIC EFFECTS FROM THE INTRAPERITONEAL USE OF SULFANILAMIDE\*

### Report of Two Cases

MARK FALCON LESSES, M.D.,† AND ARNOLD STARR, M.D.‡

BOSTON

THE use of sulfanilamide as a local therapeutic agent for the prevention or treatment of peritonitis has recently been widely advocated.<sup>1-5</sup> Although the available reports attest its value, little mention is made of toxic effects such as those so frequently described following the oral administration of this drug.<sup>6</sup> Because of the desire to attain a high local concentration, the amounts used intraperitoneally (8 to 15 gm.) have been large when compared with the amounts given in single doses either by mouth or by vein. Extremely rapid absorption from the peritoneum occurs, with resultant high blood levels of sulfanilamide that are soon followed by a drop to low values, a decline probably due to quick disappearance of the drug from the peritoneal cavity. According to most observers, the blood sulfanilamide level is elevated for about forty-eight hours, the highest peak being reached within two to twelve hours.

Toxic effects from the rapid absorption of the massive doses usually employed might therefore be anticipated even more frequently than following its use by mouth. Yet Thompson, Brabson and Walker<sup>4</sup> observed in 59 cases of acute appendicitis treated with intra-abdominal sulfanilamide that no toxic reactions beyond cyanosis occurred, except for 1 case of jaundice, which they attributed to an associated streptococcal peritonitis. On the other hand, Jackson and Coller,<sup>7</sup> although they note the beneficial results of intraperitoneal sulfanilamide therapy in peritonitis, draw attention to the higher incidence of jaundice in these patients as contrasted with those who have received the drug only by mouth. Icterus developed in 6 out of 25 patients who received intraperitoneal sulfanilamide; they attributed the icterus to liver damage.

Two cases are herewith reported in which 8.0 and 12.0 gm. of sulfanilamide were employed intraperitoneally, with resultant toxic reactions in the form of anemia and leukopenia in one case, and anemia and hepatitis in the other.

### CASE REPORTS

**CASE 1.**§ A 62-year-old woman entered the Beth Israel Hospital on February 27, 1941, with the complaint of

abdominal pain. She had been well until 2 years previously, when she developed abdominal colic that gradually increased in severity. Three months before admission, she noted pain in the left upper quadrant following meals, as well as gaseous eructations and a feeling of distention. During this same period, the patient became constipated, and there were occasional episodes of rectal bleeding. She had lost 32 pounds in weight in the 4 months preceding admission. Concomitantly, there was pallor of the skin and exertional dyspnea. A roentgen-ray examination of the large bowel at another hospital was interpreted as showing carcinoma of the colon. The past, family and marital histories were noncontributory.

The positive findings on physical examination were moderate pallor of the skin, conjunctivas and mucous membranes, and a blood pressure of 150/85. The rest of the physical examination revealed no important deviations from the normal.

The urine was free of albumin, sugar, bile or abnormalities of the sediment. The blood showed a red-cell count of 3,250,000 with a hemoglobin of 40 per cent (Sahli), and a white-cell count of 6600, with 71 per cent neutrophils, 20 per cent lymphocytes, 8 per cent monocytes, and 1 per cent basophils. There was slight achromia of the red cells, with moderate variation in the size and shape of the cells, and occasional polychromatophilia; the platelets appeared normal in number. The blood nonprotein nitrogen was 27 mg. and the total protein was 4.9 gm. per 100 cc., with an albumin of 3.04 gm. and a globulin of 1.94 gm.

For 5 days, the patient was prepared for operation with enemas, saline laxatives, intravenous glucose and saline solutions, and a low-residue diet. A transfusion of 500 cc. of citrated whole blood was given the day before operation, without undue reaction. Following transfusion, the red-cell count was 4,590,000 with a hemoglobin of 64 per cent (Sahli), and the white-cell count was 13,800 with 92 per cent neutrophils, 6 per cent lymphocytes and 2 per cent monocytes; there was slight achromia, anisocytosis and poikilocytosis of the red cells.

On the 5th hospital day, laparotomy was performed under spinal anesthesia. A malignant lesion involving the hepatic flexure of the colon was found. There was free, cloudy fluid in the peritoneal cavity, with injected and granular loops of small bowel, indicating early peritonitis. A large carcinomatous mass invaded the right retroperitoneal region, and a perforation was present in the ascending colon just below the hepatic flexure, with slight leakage of intestinal contents. Because of the peritonitis, nothing more than a cecostomy was done; this procedure employed a Pezzar catheter, which was brought out through a short oblique incision in the right lower quadrant. Eight grams of sulfanilamide powder was distributed in the peritoneal cavity, especially about the cecostomy area. The incision was closed with mass sutures of silk, and the cecostomy wound was closed with interrupted catgut sutures.

Following operation, the temperature rose abruptly to about 103°F., and the pulse rate to 120. Pyrexia and

\*From the Medical and Surgical services, Beth Israel Hospital.

†Instructor in medicine, Tufts College Medical School; associate visiting physician, Beth Israel Hospital.

‡Instructor in surgery, Tufts College Medical School; junior visiting surgeon, Beth Israel Hospital.

§We are indebted to Dr. Adolph Meltzer for permission to report this case.

tachycardia were maintained at or above these figures until death. Five hours after operation, the blood sulfanilamide level was 12.6 mg per 100 cc. A sharp drop in the red and white cells of the blood was present (Table 1), with a moderate drop in the hemoglobin but without relative neutropenia. On the day following operation, there was a further drop in the hemoglobin to 46 per cent (Sihli). The red-cell count remained about 2,500,000, and there was further leukopenia, the white cell count being 2700, with abundant granulocytes. The

which fecal material could be freely expressed into the peritoneal cavity. Within the ascending colon was a necrotic papillary tumor, 40 cm in width, completely encircling the bowel and extending above and below the papillary projections. The retroperitoneal tissues of the right lumbar gutter showed marked inflammatory changes, without free pus. No gross hemorrhage was evident. The tumor extended upward to the hepatic flexure, adhered to the head of the pancreas and was slightly fixed to the lower pole of the right kidney, ex-

TABLE 1 Laboratory Data in Case 1

DATE	RED CELL COUNT	H & H (SIL)	WHITE CELL COUNT	POLY MORPHO NUCLEARS	LYMPHOCYTES	MEGACYTES	BLOOD PLASMA	BLOOD SULFANILAMIDE
	$\times 10^6$	%	$\times 10^3$	%	%	%	ml	mg/100 cc
At admission	3.25	46	6.5	1	23	8	1	
After transfusion	4.59	64	13.8	92	6	2		
Five hours postoperative	2.60	54	4.3	82	12	6		17.6
Twenty-four hours postoperative	1.50	46	2.7	72	16			7.5

patient's condition rapidly declined and death occurred 36 hours after operation. On the day of death the non protein nitrogen of the blood was 41 mg and the total protein was 3.9 gm per 100 cc. The blood sulfanilamide reading on the morning of death was 7.5 mg per 100 cc. Later that day, several hours before death—the patient was given 40 gm of sulfanilamide intravenously and a transfusion of 500 cc of citrated whole blood.

**Autopsy.** At post mortem examination, purulence was absent but the presence of pillow of the mucous membranes, which had been noted clinically, was confirmed.

There were inflammatory changes in the peritoneum extending into the right pelvis and to the viscera contiguous with the anterior abdominal wall. One hundred cubic centimeters of reddish brown purulent foul smelling material was noted in the abdomen situated between coils of bowel and in the pelvis. A carcinomatous mass adherent to all adjacent structures was present in the ascending colon just above the cecum.

There were congestion and edema of the lower lobes of both lungs.

The mucosa of the lower two thirds of the esophagus was red and injected, and showed numerous small dilated submucosal vessels, with small patches of gross hemorrhage in some areas, and diffuse submucosal hemorrhage in others. The mucosa and muscularis of the esophagus were, however, intact throughout. There was marked dilatation of the esophagus, which contained a considerable amount of brown, foul smelling fluid, similar to that observed in the stomach.

The stomach was of normal size and contained a considerable quantity of fluid similar to that noted in the esophagus. The entire mucosa was covered by a reddish mucoid exudate, and presented beneath its surface numerous areas of submucosal hemorrhage and many small dilated vessels. These gave an appearance of diffuse hemorrhage covering the lower two thirds of the mucosa of the stomach.

The duodenum presented the same appearance so far as hemorrhage was concerned, as the gastric esophageal mucosa, but these areas were less marked and lighter in color. There was involvement of the muscularis of the third portion of the duodenum by the primary tumor, but no break through the mucosa. There was no evidence of ulcer, tumor or hemorrhage in the small intestine.

Surrounding the cecostomy wound in the colon was a small amount of purulent, fecal smelling material. There was a 1.5-cm perforation in the ascending colon, from

tending to the root of the mesentery of the small intestine where several lymph nodes were involved. The liver weighed 1740 gm and was of normal size, shape and consistence. The right lobe was adherent to the tumor mass.

On microscopic examination, some of the bronchioles showed a moderate infiltration of leukocytes and lymphocytes in the fibrous tissue comprising the submucosal layer. The alveoli of the lower lobes appeared compressed and contained small scattered collections of polymorphonuclear leukocytes without fibrin between them. There was marked compression of the alveoli of the lower portion of the lower lobe.

The liver cells showed no degenerative changes. No metastases were present.

The submucosa of the stomach contained numerous blood vessels markedly distended with blood but without free hemorrhage. The same picture was seen in the duodenum.

The primary tumor in the colon was a relatively anaplastic adenocarcinoma. The regional lymph nodes were involved by metastases.

Bone marrow from a rib was moderately cellular and contained, predominantly, cells of the granulocytic series. A moderate number of megakaryocytes were seen but nucleated red blood cells were rare. The marrow contained a considerable amount of fat but no appreciable amount of fibrous tissue. No metastatic tumor formation was present.

Post mortem bacteriologic cultures from the heart's blood showed the presence of nonhemolytic streptococci and *Escherichia coli*, whereas cultures from the abdominal fluid contained the same organisms in addition to *Clostridium welchii*.

The patient died of a blood stream infection with nonhemolytic streptococci and *Esch. coli*, and generalized peritonitis caused by a perforation into the peritoneal cavity at the site of the adenocarcinoma of the ascending colon. The anemia evidenced by this patient before death was associated with hypoplasia of the red-cell elements of the bone marrow. The hemorrhagic lesions in the intestinal tract were terminal.

**Comment.** In this case, death was primarily due to septicemia and peritonitis from carcinomatous perforation of the colon but the development of marked anemia and leukopenia within 5 hours after laparotomy and intra peritoneal instillation of 80 gm of sulfanilamide must be ascribed to the toxic action of this drug. The bone

marrow was hypoplastic in red-cell elements. Although some of this hypoplasia undoubtedly antedated operation, the peripheral blood changes indicated that further depression occurred following the use of sulfanilamide. The marrow showed abundant cells of the granulocytic series, and this too was reflected in the blood stream in the maintenance of an adequate percentage of neutrophils. However, the white blood cells and the absolute number of neutrophils progressively declined, indicating failure of delivery of these cells to the blood stream from the marrow. Other possible mechanisms of blood destruction or blood loss were not operative since the septicemia was caused by nonhemolytic streptococci and *Esch. coli*, and

sediment. The blood nonprotein nitrogen was 26 mg. per 100 cc., and the icteric index 9.

Several hours after admission, laparotomy was performed under spinal anesthesia. The peritoneal cavity was filled with turbid brown fluid, which was aspirated and subsequently found to contain *Esch. coli*. An adherent cystic mass, 20 cm. in diameter, arising from the right ovary filled the pelvis. Its wall was congested and necrotic in patchy areas, and purulent fluid oozed from several perforations. The cyst was freed and removed. Its bed contained a mass of greenish-gray membranous tissue resembling the wall of an abscess. In view of the extensive nature of the infection, 12 gm. of

TABLE 2. Laboratory Data in Case 2.

DATE	RED-CELL COUNT × 10 <sup>9</sup>	HEMOGLOBIN (SAHLI) %	WHITE-CELL COUNT × 10 <sup>3</sup>	POLY-MORPHO-NUCLEARS %	LYMPHO-CYTES %	MONO-CYTES %	ICTERIC INDEX	BLOOD SULFANILAMIDE mg./100 cc.	URINE BILIRUBIN
2/15*		96	8.6	73	19	6	9		0
2/16†	3.70	68	15.1	94	4	2	9	4.5	0
2/17	3.10	64	14.2	91	7	0	35	7.0	0
2/18	4.20	65	15.4	93	6	2	30		++++
2/19	3.64	66	11.9	91	8	1	25		
2/20	3.30	66	13.2	86	11	1	18	Trace	+++
2/21	3.35	72	10.6	76	18	4	18	0.0	+++
2/24‡	3.60	78	23.7	83	9	-	15		0
2/26	4.10	70	26.8	83	16	1			0
2/27	3.75	72	13.9				13		
3/1	3.75	74	15.4	79	10	8	8		0
3/6§	3.25	68	15.3						0
3/10¶	3.74	76	7.7	84	7	5			+
3/12	4.05	76					6		

\*Preoperative.  
†Postoperative, following 500-cc. transfusion of whole blood and 5.0 gm. sodium sulfathiazole and 6.0 gm. sulfanilamide intravenously.  
‡After 500-cc. transfusion of whole blood.  
§After posterior colpotomy.  
¶After 500-cc. transfusion of whole blood.

the submucosal gastrointestinal hemorrhages were terminal and inadequate to account for the anemia.

Five hours after operation, the blood sulfanilamide level had risen to 12.6 mg. per 100 cc., indicating that rapid absorption had occurred. The patient also received 4.0 gm. of sulfanilamide intravenously, but this was given well after the onset of the anemia and shortly before death, so that it could not have contributed materially to the toxic reaction.

CASE 2. A 40-year-old woman entered the Beth Israel Hospital on February 15, 1941, complaining of right-sided lower abdominal pain of 6 hours' duration. One month prior to entry, there had been an attack of lower-right-quadrant pain, which subsided without treatment but was followed by symptoms of so-called "grippe," from which complete recovery had occurred. Twenty years previously, there had been an operation for disease of the right ovary.

Physical examination showed a dusky pallor of the skin. The temperature was 105°F., and the pulse rate 158. The abdomen was tense, spastic and diffusely tender. Vaginal examination revealed a moderate whitish discharge, no pain on motion of the cervix, and no abnormalities of the vaults. On bimanual examination, a firm, large, tender abdominal mass was felt in the midline, separate from the uterus. The blood pressure was 160/100. The heart was moderately enlarged to the left and regular in rhythm, with a faint, blowing apical systolic murmur. The lungs showed no abnormalities. The remainder of the physical examination was not noteworthy.

The blood showed a hemoglobin of 96 per cent (Sahli) and a white-cell count of 8600. The urine was acid, with a specific gravity of 1.015, and negative for albumin, sugar and bile, with a trace of acetone and with a normal

sulfanilamide was placed in the peritoneal cavity, and the wound was closed without drainage with interrupted silk-mass sutures. An intravenous infusion of 500 cc. of plasma was given during the operation.

After operation, the pulse and temperature persisted at high levels for about 5 days. In the 24 hours subsequent to laparotomy, the following therapy was administered: 2000 cc. of plasma, 500 cc. of citrated whole blood, 6.0 gm. of sulfanilamide intravenously and 5.0 gm. of sodium sulfathiazole intravenously. On the 2nd postoperative day, 2.0 gm. of sulfathiazole was administered by mouth. No additional chemotherapy was used.

Deep jaundice of the skin and mucous membranes developed 36 hours after operation. At the same time, signs of bilateral pneumonia became apparent both by physical and roentgen-ray examinations. Coincident with the appearance of the jaundice, there was a moderate drop in the red-cell count (Table 2) and the development of a marked bilirubinuria. The administration of sulfonamide compounds was immediately stopped, and although blood studies at intervals of 4 hours showed no further hemolysis, a transfusion of 500 cc. of citrated whole blood was given to return the blood to more normal levels. With the cessation of chemotherapy, no further anemia developed, and there was a gradual decline of the icteric index from its high value of 35 on the 2nd postoperative day to normal on the 14th, with disappearance of bilirubin from the urine. The pneumonia gradually subsided, and by the 6th postoperative day, the patient's condition was good, but the temperature had not quite returned to normal. From this time on, the convalescence was complicated by the development of a pelvic abscess, which manifested itself by leukocytosis and pyrexia and, later, by the appearance of a pelvic mass. This was drained through the posterior cul-de-sac on the

22nd postoperative day. A considerable quantity of foul, yellowish green pus was evacuated from the abscess cavity. Thence onward, recovery quickly ensued, and the patient left the hospital in good health on the 32nd day after entry.

**Comment.** This patient, critically ill with diffuse peritonitis, recovered following excision of a ruptured, gangrenous ovarian cyst, and the intraperitoneal instillation of 120 gm of sulfanilamide. However, jaundice and anemia developed as a toxic reaction. The intensity and duration of the bilirubinuria indicated that the jaundice was primarily due to toxic hepatitis, for the moderate hemolysis of the blood could have contributed only a small amount of the increased bilirubin. The blood sulfanilamide level rose to 4.5 mg per 100 cc on the morning following operation, and to 7.0 mg per 100 cc on the next day, with complete disappearance from the blood stream by the 6th postoperative day.\*

### Discussion

During the past year, the value of the intraperitoneal use of sulfanilamide in peritonitis has been stressed by several authors, with emphasis on the lack of toxic reactions. Jackson and Collier,<sup>7</sup> however, have already remarked on the increased incidence of jaundice, and the 2 cases herein reported are further evidence of the toxicity of sulfanilamide when given intraperitoneally in large doses. There has been a gradual replacement of sulfanilamide by sulfapyridine, sulfathiazole and other sulfonamide compounds for oral and parenteral therapy, not only because of their greater efficacy but also because of apparent decreased toxicity. The same consideration may well apply to the intraperitoneal application of sulfanilamide, a drug initially selected because of its greater solubility. But this very property causes such rapid absorption that Jackson and Collier believe it doubtful whether the primary local effect lasts more than one or two hours. Throckmorton<sup>8</sup> also found that after six to twelve hours there was no gross evidence of sulfanilamide placed in the peritoneum of rats, in contrast to sulfathiazole, which remained grossly visible for three to six days. This greater solubility not only militates against prolonged local action, but also exposes the entire organism to undesirable reactions. Even the inflamed peritoneum rapidly absorbs sulfanilamide, as is well shown by the speedy elevation of the blood level. Although blood levels are not an index of continued intraperitoneal activity, the peritoneum is such an effective absorbing surface that the duration of local action of a soluble substance like sulfanilamide is necessarily short.

The systemic effect of intraperitoneal sulfanilamide approaches that seen following intravenous administration because of the speed with which high blood levels are reached, and there is prob-

bly a more toxic action on the liver than with oral administration because of the site of application. Jackson<sup>9</sup> found a 30 to 40 per cent higher level of sulfanilamide in the portal blood of dogs that had received intraperitoneal sulfanilamide as compared with the level in jugular blood, and suggested that the jaundice might be due to liver damage caused by these high portal levels. In this connection, Bieter and his co-workers<sup>10</sup> have shown in chickens that, even with orally administered sulfonamides, there is selective concentration of sulfanilamide in the liver, as contrasted with sulfapyridine or sulfathiazole.

Goodwin and Findlay,<sup>11</sup> in an experimental investigation of locally applied sulfonamide drugs, pointed out that it is possible to obtain an effective concentration in the blood with locally applied sulfanilamide but not with sulfapyridine or sulfathiazole. The latter substances are removed too slowly from the site of application for any measurable blood concentration to be produced. Throckmorton's<sup>8</sup> experiments on rats, however, indicate that sulfapyridine may be injurious to the peritoneum in contrast to sulfathiazole, which does not cause peritoneal damage and which furthermore has such delayed absorption that the local defense mechanism is augmented by the foreign-body reaction. On the basis of the solubilities and available evidence, therefore, one would be justified in using sulfathiazole rather than sulfanilamide if prolonged intraperitoneal action is desired with minimal general effects.

### SUMMARY

Two cases are reported in which the intraperitoneal use of sulfanilamide in massive single doses caused anemia, leukopenia and hepatitis.

The substitution of a less soluble sulfonamide such as sulfathiazole for intraperitoneal use is suggested.

### REFERENCES

1. Herrell W F and Brown A E. Local use of sulfonamide compounds in the treatment of infected wounds. *Proc Staff Meet Mayo Clin* 15:61-75 1940.
2. Mueller R S. Use of powdered crystaline sulfanilamide in surgery. *J A M A* 116:399 1941.
3. Rosenberg S and Wall N M. Treatment of diffuse peritonitis by direct intraperitoneal introduction of sulfanilamide. *Surg, Gynec & Obst* 72:578 1941.
4. Thompson J F, Bryson J A and Walker J M. The intraperitoneal application of sulfanilamide in acute appendicitis. *Surg, Gynec & Obst* 72:727 1941.
5. Long L W and Dees J G. Local use of sulfanilamide. *Surgery* 9:878-887 1941.
6. Long P H, Haviland J W, Edwards I B and Bliss F A. Toxic manifestations of sulfanilamide and its derivatives with reference to their importance in course of therapy. *J A M A* 115:364 365 1940.
7. Jackson H C and Collier F A. The use of sulfanilamide in the peritoneum. *Program of the American Medical Association* Cleveland Ohio June 2-6 1941. P 51.
8. Throckmorton T D. The peritoneal response to powdered sulfonamide compounds: experimental studies. *Proc Staff Meet Mayo Clin* 16:423-425 1941.
9. Jackson H C. Intraperitoneal sulfanilamide. *Ann Surg* 113:107 1941.
10. Bieter R N, Baker A B, Peaton J G, Shaffer J M, Seery T M, and Orr B A. Nervous injury produced by sulfanilamide and some of its derivatives in the chicken. Preliminary report. *J A M A* 116:1231-1236 1941.
11. Goodwin L C and Findlay G M. Absorption and excretion of sulfonamides applied locally: observations in rabbits. *Lancet* 1:691 1941.

\*The concentration of sulfanilamide in this patient rose to a level intravenously during the twenty-four hours subsequent to operation may well have contributed to the toxic hepatitis, but was probably not the precipitating factor. There is some doubt as to the interval between the intravenous administration of the drug and the onset of the jaundice, and by the 1% incidence of hepatitis (0.6 per cent in a series of 1000 cases as reported by Long and Starr) following the oral modes of administration, sulfanilamide

## CLINICAL NOTE

TREATMENT OF  
TRICHOMONAL VAGINITIS  
WITH ACETARSONE TAMPONS

JOE V. MEIGS, M.D.\*

BOSTON

IN 1933, Gellhorn<sup>1</sup> advocated the use of acetarsone (Stovarsol) in a powder blower for the treatment of vaginitis due to *Trichomonas vaginalis*. His results were superior to any he had obtained by other methods. Acetarsone is an arsenical and as such may be considered moderately dangerous, but no untoward results were present in Gellhorn's series.

This treatment is usually given in the physician's office and necessitates frequent visits. Hence, it seemed advisable to devise a means for carrying out the treatment at home. This appeared possible by the use of tampons (Tampax) infiltrated with acetarsone, and arrangements were made with a pharmaceutical house for their preparation. It was hoped that these medical tampons would absorb the discharge and control the infection. Since 1938, a number of patients have been treated by this method.

The tampons† are made up by dusting each with  $1\frac{1}{2}$  gr. of acetarsone; in addition, a tablet containing  $\frac{1}{2}$  gr. of acetarsone, 2 gr. each of glucose, lactose and boric acid,  $\frac{1}{2}$  gr. of starch,  $\frac{1}{4}$  gr. of sodium bicarbonate and  $4/10$  gr. of tartaric acid is placed on the top of each tampon. The pH of the solution of this tablet is approximately 3.0.

In each case, after the diagnosis had been made by examination of a drop of discharge, diluted with two or three drops of warm water, under the high-dry lens of the microscope, the patient was treated with an acetarsone-powder insufflation and then was given the medicated tampons to use at home. For the first week, the tampons were used every night or were inserted in the morning and removed at night. The latter method prevented the discharge from irritating the vulva while the patient was on her feet. At the end of a week, a warm douche of sodium perborate (one tablespoonful to a quart of warm water) was taken, to remove the accumulated powder. During the next week, the tampons were inserted every other day, and during the following week, they were used every third day, the weekly douches

being repeated. This went on until the next menstrual period. The medicated tampons were used throughout the period, but after it had ceased, the treatment was omitted for a few days and a smear taken during an office visit. If this was positive, the same treatment was repeated. If the smear was negative, the patient was told to use a tampon twice a week, with a sodium perborate douche at the end of the week. If, after the next period, the vagina was still free from the organism, treatment was stopped.

As part of the treatment, patients were advised to wipe the anus after a bowel movement from front to back and not from back to front, for it is possible that *Trich. hominis* may infect the vagina. Furthermore, all patients were advised to wash their hands carefully both before and after going to the toilet. Absolute cleanliness is necessary, since reinfection of the vagina and vulva may result from chance contamination.

Thirty-nine patients were treated. The duration of the infection was a matter of days in some and of months or years in others. Of the 39 patients, 33 were given one series of treatments; 5, two series; and 1, four series. In 19 cases, the treatment was successful, that is, a negative smear that remained negative after two successive menstrual periods was obtained. In 10 cases, negative smears were not obtained but the patients obtained considerable relief of symptoms; in 6, there was a complete failure. In 4 cases, the treatment was successful the first time but the disease recurred. In 4 patients who had been treated by other methods, the tampon treatment was successful.

Of the 39 patients treated, 26 considered the treatment satisfactory, 6 thought that it was not, and 7 were not sure whether it was helpful or not. In no case was any reaction to arsenic noted. In only a few cases was the treatment given up because of the patient's inability to use the tampons; however, the method was seldom used in young girls.

## SUMMARY

The use of medicated tampons containing acetarsone (Stovarsol) is a satisfactory method for the home treatment of patients with vaginitis due to *Trichomonas vaginalis*.

Of 39 patients treated in this way during the past three years, 19 were permanently cured and 7 more were symptomatically relieved.

264 Beacon Street

## REFERENCE

1. Gellhorn, G. The treatment of trichomonas vaginitis with acetarsone (Stovarsol). *J. A. M. A.* 100:1765, 1933.

\*Instructor in surgery, Harvard Medical School; chief of Gynecologic Service, Massachusetts General Hospital.

†The medicated tampons are manufactured by the Allen Laboratories, Incorporated, New Brunswick, New Jersey, and are marketed under the trade name, Allen Brand of Tampons with Acetarsone (Stovarsol).

## MEDICAL PROGRESS

## NUTRITIONAL DEFICIENCIES IN RELATION TO THE DIGESTIVE TRACT

CHESTER M. JONES, M.D.\*

BOSTON

WITH the realization that specific food substances may affect in a striking manner the production of such diseases as scurvy, rickets, pernicious anemia and similar conditions, much of the investigative work of recent years has concerned itself with an attempt to clarify the action of specific nutritive components on tissue and organic function. The availability of various specific vitamins has further led to numerous observations on the effects of these substances on individual diseases, such as pellagra, and on the manifestations of more general pathologic conditions. Because, in specific deficiency states, almost miraculous clinical changes may be obtained by the use of replacement therapy, there has been a natural, although poorly directed, application of these results to a large number of conditions without critical or well-controlled studies. Such therapeutic enthusiasm, although understandable, is to be regretted because much of it involves wishful thinking and leads to needless and frequently useless forms of therapy at moderate or great expense to the patient. It is pertinent, therefore, to present a few of the numerous studies on the relation between specific nutritional factors and digestive-tract function that have been made by various observers.

As Youmans<sup>1</sup> has been careful to point out, there is very little scientific evidence of the exact effect that vitamin deficiencies exert on disease, and hence little justification for much of the widespread use of vitamins as therapeutic agents in a great number of illnesses. As he states, there is good reason to believe that vitamin deficiencies do occur as complications of many diseases and modify unfavorably their course and outcome. For the present, however, the influence of vitamin deficiencies must be considered to be that which might reasonably be expected from poor general nutrition. There is little reason to doubt that mild or subclinical pellagra has an effect on the course of other illnesses, but no specific information is as yet available of the exact effect that such a deficiency produces. The fact that no good clin-

ical test for most hypovitaminoses exists gives most deductions a speculative rather than a truly scientific value.

Further limitations to the value of clinical or animal investigations are obvious when one remembers, as Spies and his group<sup>2</sup> point out, that vitamin B, which was formerly considered a single substance, is probably composed of twelve or more separate factors, each of which together with unknown substances contributes to the total effect of various therapeutic agents, such as yeast, wheat germ and liver extract. The wisdom of general replacement therapy is borne out by his experiences at the Hillman Hospital, where studies were made on a group of 1250 consecutive cases of malnutrition. In addition to specific vitamin lacks, it was noted, for example, that a large number of persons received as little as 50 per cent of the estimated energy requirements, and in many cases the protein intake was too low to maintain nitrogen equilibrium. Nearly all the patients received substandard amounts of calcium, phosphorus and iron, and none obtained standard amounts of all three elements. Spies and his collaborators stressed the value of administering water-soluble and fat-soluble vitamins together, rather than as individual prescriptions, as the most useful method of treating most deficiencies. Mackie et al.,<sup>3</sup> in an excellent review of vitamin deficiency in gastrointestinal disease, stress the point that symptoms may be produced because of certain disturbances of normal body chemistry due to avitaminosis without demonstrable clinical evidence of disease except in a few cases. They also point out the frequently forgotten fact that many of the dietary regimes in vogue for the treatment of diseases of the digestive system are open to grave suspicion so far as adequacy of food constituents is concerned. A practical consideration of some of the causes leading to avitaminosis is indicated in a paper by Rosenblum and Jolliffe,<sup>4</sup> who observe that various therapeutic maneuvers very definitely contribute to vitamin lack or interfere with the normal utilization of the vitamins that are being administered. In the presence of alkali therapy, orally administered ascorbic acid, thiamin chloride, riboflavin and perhaps other vitamins are inactivated or destroyed. Absorption of large amounts of these and other vitamins may be associated with the use of col-

Reprints of articles in this series are not available for distribution, but the articles will be published in book form. The current volume is *Medical Progress: Annual, 1940* (Springfield, Illinois: Charles C. Thomas Company, Inc., \$4.00).

\*Clinical professor of medicine, Harvard Medical School; physician, Massachusetts General Hospital.

loidal aluminum hydroxide or of magnesium trisilicate. Oral treatment with the fat-soluble vitamins may definitely be adversely affected by the associated ingestion of liquid petrolatum. From the surgical aspect, a too liberal use of fluids parenterally, in the form of glucose solutions, contributes distinctly to the increased elimination of members of the vitamin B complex, and is particularly undesirable when operative procedures on the gastrointestinal tract have been performed. A similar danger prevails in other states in which parenteral feeding is necessary.

Numerous references to the effect of already existing gastrointestinal disease on the production of dietary deficiencies are to be found. Brown,<sup>5</sup> along with many others, mentions the occurrence of various deficiency states secondary to prolonged vomiting, diarrhea and the like. In addition, he is authority for the statement, which is probably correct, that actual ulcerative disease of the colon may occur as the aftermath of a poorly balanced diet, particularly when associated with unusual stress, such as intercurrent infection or pregnancy. He mentions the finding of frank ulcerations of the colon resulting from such conditions. Exact proof for such statements is still lacking, but there can be no doubt that at times profound organic changes occur at different levels of the digestive tract as the result of general or specific malnutrition. Bean and Spies<sup>6</sup> mention their findings in 100 persons studied in an area of endemic pellagra, beriberi and riboflavin deficiency, who developed such symptoms as a complication of chronic diarrhea. They also note that chronic diarrhea itself predisposes to the development of deficiency syndromes because of increased loss of nutritive products and decreased absorption, and they also point out that if the diarrhea is relieved, even without vitamin therapy the secondary deficiency is usually improved. In their article, these authors advocate, as many others do, the use of parenteral injections of crystalline vitamins in the presence of active diarrhea because these substances are lost when given orally. They insist, however, that in most cases parenterally given vitamin preparations do not take the place of a high-protein, high-calorie diet, together with large doses of nicotinic acid, thiamin hydrochloride and riboflavin. They suggest the daily use of between 500 and 1000 mg. of nicotinic acid amid, 10 to 50 mg. of thiamin hydrochloride, and 2 to 10 mg. of riboflavin during the acute manifestations of deficiency.

Among the objective changes in the alimentary tract that are properly attributed to avitaminosis, Wilbur<sup>7</sup> mentions the symptoms of anorexia and diarrhea, abnormalities in function, such as achlorhydria, alterations of the motor and absorptive activities of the intestine, and such lesions as stoma-

titis, glossitis, proctitis, and atrophy and inflammation of the gastric and intestinal mucosa. Although proof of the exact etiology of any or all of these changes is still incomplete, he quite rightly stresses the benefit of careful inspection of the oral cavity, analysis of gastric contents, x-ray films of the alimentary tract with particular reference to the small intestine, and other searches for vitamin deficiency, such as the demonstration of peripheral neuritis, edema and night blindness. These conceptions are not new but are worthy of repetition.

That the function of the bowel is seriously interfered with in the presence of deficiency disease has been noted by various observers. For example, Groen<sup>8</sup> has shown that the absorption of glucose from the small intestine is distinctly interfered with in various deficiency conditions and can be restored to normal by proper replacement therapy. Similarly, Beams, Free and Glenn,<sup>9</sup> in studying patients with pellagra and nontropical sprue, found impaired absorption of galactose, with improvement, at least in patients suffering from pellagra, following specific therapy. They also noted that several cases of rosacea keratitis, which responded to riboflavin therapy, gave indication of increased galactose absorption that later improved, with the disappearance of the skin lesions.

Changes in the gastric mucosa in numerous deficiency diseases have been mentioned by various investigators and need only be noted briefly to indicate the effect of such a change in rounding out the vicious circle of malnutrition. X-ray evidences of disturbed motor or absorptive function in the small bowel have been noted by numerous investigators in patients suffering from various forms of dietary lack. These changes, for the most part, are in association with diarrheal states and are demonstrable as changes in tone, caliber and motility of the small bowel or as complete disappearance of the distinctive mucosal markings. Evidence has been produced that they may be effected by protein deficiency or by lack of various members of the B complex. A too exact interpretation of the x-ray findings mentioned by Kantor,<sup>10</sup> Mackie,<sup>11</sup> Golden,<sup>12</sup> Tyler<sup>13</sup> and others should not be attempted at the present time. Perusal of various articles that have appeared in recent years on this particular phase of small-bowel disturbance leads to the conclusion that strict deductions about functional or cellular changes in the small bowel, as evidenced by x-ray studies, should be made with extreme caution. That such changes may be seen in idiopathic steatorrhea, advanced ulcerative colitis, tropical sprue, infantile celiac disease, pellagra and other conditions is undoubtedly true. As Mackie properly points out, however, such a "deficiency pattern" may occur in a variety of conditions, such as nephrosis, diabetes

insipidus, diseases of the mesenteric lymphatics, abdominal cancer and certain jaundiced states. He also mentions a most interesting fact, which as yet is unexplained—namely, that the same alterations in mucosal pattern can be observed in the intestine of the normal newborn infant. Since these changes disappear early in life and since degeneration of the nerve cells of the myenteric plexuses in adults presenting the deficiency pattern has been demonstrated, these modifications of the normal mucosal pattern of the small bowel are probably the result of interference with the intrinsic nervous mechanism. Confirmation of such a hypothesis, in my experience, may be found in the histologic demonstration of profound atrophic changes existing in Auerbach's and Meissner's plexuses in patients dying with advanced pellagra. According to Mackie and others, such changes can usually be reversed by the enthusiastic administration of the B complex in the form of crude liver extract and yeast. The more concentrated preparations, as a rule, are less effective or may be ineffective. A detailed description of the radiologic changes in the small bowel supposedly secondary to vitamin B deficiency is given by Golden,<sup>12</sup> but it should be stated that as yet not all radiologists are in entire agreement with this author.

An interesting and moot question is that of the interrelation of deficiency disease and resistance to infection. Riddle, Spies and Hudson<sup>14</sup> have made certain interesting observations on 150 selected cases of pellagra, riboflavin deficiency and beriberi. Before, during and after treatment, the bacterial flora of the lesions associated with various vitamin deficiencies was investigated, and certain immune reactions were studied. The lesions at the corner of the mouth characteristic of riboflavin deficiency were found to contain pure or nearly pure cultures of certain strains of *Staphylococcus aureus* in 80 per cent of the cases, and in the remaining 20 per cent *Streptococcus hemolyticus* predominated. Following the oral or intravenous administration of riboflavin or of substances rich in it, the fissures healed rapidly, and the organisms were no longer demonstrable. A study of the bacterial flora of the conjunctival sacs was made in cases of deficiency disease with associated conjunctivitis, and hemolytic strains of *Staph. aureus* were found to predominate in half of 30 cases. In addition to large numbers of Vincent's organisms, two thirds of the patients showing ulcerations of the tongue, gums or buccal mucosa yielded hemolytic streptococci, and the remaining third showed hemolytic strains of *Staph. aureus*. Following specific therapy with anti-pellagic substances, the bacterial flora, including the Vincent's organisms, promptly disappeared.

Apparently, a low complement titer existed in many of the acutely deficient patients and rose coincidentally with clinical improvement. In the whole blood of acutely deficient patients, there was a distinct depression in the bactericidal power for *Staph. aureus*, but little, if any, diminution was noted in the subclinical or mild cases of deficiency. Chapman and Harris<sup>15</sup> observed that monkeys maintained on certain vitamin-deficient diets developed a tendency to oral lesions accompanied by an increase in the fusospirochetal flora. This was apparently in association with diets deficient in parts of the vitamin B<sub>2</sub> complex. Those animals on an adequate stock diet tended to resist the artificial implants of the fusospirochetal flora under the severest of test conditions. The presence of glossitis, buccal aphthae and similar changes is a well-known accompaniment of various deficiency states, and the response to certain members of the vitamin B complex is now generally recognized. It is still essential, however, to stress the fact that careful observation of the tongue frequently yields a clue to an otherwise subclinical deficiency condition existing in patients requiring surgery of the gastrointestinal tract and may indicate the need for more than average care in the preoperative preparation. The report of Manson-Bahr<sup>16</sup> includes a very complete discussion of glossitis, with particular reference to vitamin B<sub>2</sub> deficiency in pellagra, sprue and allied states. Among other interesting facts, the author mentions a study of 500 cases of tropical sprue seen in India, Burma and other oriental countries. In three fourths of these patients, striking glossitis was one of the most prominent symptoms even when no anemia was observed. Improvement following the use of nicotinic acid was rapid, and corresponded to the results obtained in pellagra and certain other conditions. Manson-Bahr also points out the important consideration that changes in the buccal mucosa and tongue may be the result of nicotinic acid or riboflavin deficiency incident to an underlying pathologic condition.

Numerous studies on individual vitamin requirements and deficiency are of interest. It is generally admitted that the absolute requirements of the various specific food substances are still not known. The work of Elsom and Machella<sup>17</sup> on the intake of thiamin and its relation to other dietary constituents in food selected by normal subjects is of interest. Observations on a small group of normal subjects showed that the average daily intake of thiamin exceeded the theoretical requirement by 40 per cent, but the individual intake ranged from 6 to 115 per cent above the so-called "maintenance need." There was a tremendous variation of thiamin intake on individual days in the



The relation between vitamin C deficiency and peptic ulcer still continues to be studied. That low plasma levels of ascorbic acid are commonly encountered in patients suffering from peptic ulcer is well known, and there is every reason to believe that this lack is occasioned by dietary restrictions rather than that the vitamin deficiency itself has anything to do with the etiology of gastric or duodenal ulceration. Once established, however, such a deficiency may retard healing, and for this reason, as in other chronic diseases, it is essential to maintain a balanced diet, and the administration of optimum doses of vitamin C may assume real clinical value as a detail in ulcer therapy. The frequency with which vitamin C lack exists in gastric disease is illustrated by the dietary histories obtained by Ludden and his group<sup>34</sup> in a number of patients selected from the gastrointestinal and surgical clinics of the Bellevue Hospital. Dietary histories of this group of patients revealed that voluntary or prescribed diets had been very low in vitamin C. Twenty-three of 28 patients had gastric lesions; of the entire group, 1 had frank clinical scurvy, and 26 had subclinical scurvy, as indicated by laboratory data. In these patients, doses ranging from 1.5 to 11.4 gm., given from three to seventeen days, were necessary to bring about "saturation." A maintenance dosage of as high as 200 mg. daily was needed in a patient with a total gastrectomy, but other patients studied with gastric lesions conformed to the usual accepted maintenance requirements. Field et al.<sup>35</sup> report on their findings in 58 patients with peptic ulcer. They demonstrated in 29 patients that the plasma ascorbic acid values were below 0.5 mg. per 100 cc.; 10 out of 12 who were admitted to the hospital with hemorrhage had values below 0.4 mg. per 100 cc. The authors are probably correct in ascribing significance to the fact that in 2 patients in this latter group, bleeding occurred after they had been maintained on an ulcer regime for eighteen and twenty-six days respectively. Field calls attention to the need for vitamin C therapy as a valuable adjunct in the treatment of peptic ulcer and again stresses the fact that alkali therapy in ulcer patients may contribute to the deficiency in this vitamin and in vitamin B<sub>1</sub>. Ingalls and Warren<sup>36</sup> present even more striking figures so far as the actual plasma levels of vitamin C in patients with ulcer are concerned. Eighteen out of 20 patients had low plasma values for this vitamin. Six, whose histories included previous hemorrhages, had blood levels of 0.2 mg. per 100 cc. or less. Further evidence that deficiency diseases are usually multiple is found in the report from the Hillman Hospital<sup>37</sup> on blood and plasma ascorbic acid concentrations in patients with pellagra and associated deficiency diseases. Marked reduction

in blood values was found in many of the group studied, and the comment is made that these studies were carried out at a period when leafy vegetables and berries had been available to the patients for some time. In all probability, much greater deficiencies of vitamin C could have been demonstrated in the winter months.

The relation between the fat-soluble vitamins and disturbances of the gastrointestinal tract has been the basis of some studies. The absorption of carotene, the precursor of vitamin A, was studied by means of isolated intestinal loops by Irvin, Kopala and Johnston.<sup>38</sup> In the absence of bile or pancreatic lipase, only insignificant amounts are absorbed in the small bowel, but the addition of either or both of these substances affects absorption materially, and the addition of pure bile salts still further increases the amount of carotene absorbed. Previous reports on the inhibitory effect of mineral oil on the absorption of carotene are confirmed. May and McCreary<sup>39</sup> measured the amount of absorption of vitamin A in infants and children during various stages of celiac disease, or in children with the celiac syndrome secondary to other disorders. A low rise in the level of vitamin A in the vitamin-absorption test was a constant feature of celiac disease, and a similar finding was frequently observed in other conditions simulating this disease. Although not diagnostic of celiac disease, the test for vitamin A absorption described by these authors is helpful in following the clinical progress of recovery from celiac disease, since vitamin A absorption appears to return to normal when cure is complete. The level of blood carotene in celiac disease also seems to follow the clinical course of the disease, being low during the active stage and rising during improvement. Interference with the rise in plasma vitamin A following the ingestion of this substance was also noted by Ralli and his collaborators<sup>40</sup> in patients with liver disease and is in keeping with the finding of a low concentration of the vitamin, as previously noted in cirrhotic livers.

Studies on the effect of vitamin A deficiency on gastric function by Dyer and Roe<sup>41</sup> and by Herrin<sup>42</sup> indicate that lack of this vitamin does not, in animals, diminish the secretory power of the gastric cells or, to any important degree, the motility of the stomach. Some enthusiastic comments on the clinical use of vitamin A, with resulting improvement of gastric secretion in cases of achlorhydria, and more particularly in the successful treatment of peptic ulcer, are to be found in the reports of Földes and Vajda<sup>43</sup> and of Seelig.<sup>44</sup> The studies, although interesting, are far from convincing.

The keratinization of squamous-cell mucous membranes and the proliferation of epithelial cells

have been noted by various investigators of deficiency of this fat-soluble vitamin. The finding of proliferative changes in the columnar cells of the mucosal lining of the stomach in rats by Fridericia et al.<sup>45</sup> in the presence of vitamin A deficiency is therefore of some interest. Of particular significance are the observations that, in their experiments, gastric mucosal lesions occurred in animals kept on alternating deficient and normal diets for many weeks, but that restoration to a normal diet for a year reversed the changes that apparently had taken place in most of the animals. A somewhat similar study by Beck and Peacock<sup>46</sup> demonstrated that animals kept on a vitamin A deficient diet for a year developed ulcerations and papillomatous lesions of the forestomach. No alteration in intestinal permeability to bacterial toxins could be demonstrated, however, by Stryker and Janota<sup>47</sup> in animals on prolonged vitamin A deficiencies.

Abels et al.<sup>48</sup> found low plasma levels for vitamin A in the majority of patients with gastrointestinal cancer, but believed that this could be explained on the basis of an inadequate ingestion and absorption of the vitamin or an associated hepatic dysfunction so far as the storage of vitamin A or its formation from carotene was concerned. The fact that the plasma levels of vitamin A could be increased in these patients by the administration of yeast and lipocain, which are free of carotenoids, can probably be explained on the basis of the lipotropic action of these substances. It is also possible, however, that these patients presented other deficiencies due to inadequate food intake, and that the administration of yeast resulted, among other things, in better intestinal absorption.

The whole problem of hypovitaminosis of all fat-soluble vitamins caused by steatorrhea is presented in unusually complete form in the report of Albright and Stewart.<sup>49</sup> These authors emphasize the fact that pan-fat-soluble vitamin deficiency should be looked for in all cases of chronic diarrhea, regardless of the presenting symptom, and that when possible these patients should be given fat-soluble vitamins in fat-free vehicles, to obtain maximum dosage and maximum absorption. Such a consideration is of particular value in diseases like ileitis and ulcerative colitis, in which, as Mackie, Albright and others have demonstrated, a prothrombin lack with subsequent spontaneous bleeding may be a major clinical feature. That general nutritional deficiency states may include evidence of vitamin K lack, as well as that of other fat-soluble vitamins, is indicated by the study of Warner, Spies and Owen.<sup>50</sup> Forty-eight patients seen in the nutritional clinic of the Hill-

man Hospital with evidence of deficiency of one or more of the factors of the vitamin B complex were observed with relation to the prothrombin level and compared with a series of 37 patients on the Medical Service of the Iowa University Medical School. In both groups, moderate hypoprothrombinemia was demonstrated, a higher percentage being found in the patients seen in the northern clinic. The findings did not seem to be the result of vitamin K deficiency, however, in most cases, since large doses of this vitamin did not influence the prothrombin level. It was believed that the subnormal prothrombin production was rather the result of general debility than of nutritional deficiency alone.

\* \* \*

It is obvious that significant additions are being made gradually to information regarding the relation between nutritional disturbance and the function of the digestive tract. In the absence of easily applied clinical tests for avitaminoses and in the presence of many empty spaces in knowledge of the pathologic physiology associated with deficiency disease, it is the part of wisdom to treat any condition of deficiency as one with multiple components by means of those easily available food substances that can be readily obtained and taken orally. In certain cases, parenteral therapy is, of course, indicated, but every attempt should be made to utilize the oral administration of substances such as yeast, adequate amounts of protein and a really well-balanced diet.

## REFERENCES

- 1 Youmans J B. The influence of vitamin deficiencies on other diseases. *Ann Int Med* 13 980-986 1939
- 2 Spies T D, Swain A P, and Grant, J M. Clinically associated deficiency diseases. *Am J M Sc* 200 536-541, 1940
- 3 Mackie, T T, Eddy W H, and Mills M A. Vitamin deficiencies in gastrointestinal disease. *Ann Int Med* 14 28-41, 1940
- 4 Rabinowitz L A, and Joffe N. The oral manifestations of vitamin deficiencies. *J A M A* 117 2245-2248, 1941
- 5 Brown, P W. Dietary deficiency in gastro-intestinal diseases. *Mil Surgeon* 84 375-377, 1939
- 6 Bean W B and Spies, T D. Vitamin deficiencies in diarrheal states. *J A M A* 115 1078-1084, 1940
- 7 Wilbur, D L. The effects of vitamin deficiency on the gastrointestinal tract. *Am J Digest Dis* 6 610-617 1939
- 8 Green J. The absorption of glucose from the small intestine in deficiency disease. *New Eng J Med* 218 247-253 1938
- 9 Beams, A J, Free, A H, and Glenn, P M. The absorption of galactose from the gastro-intestinal tract in deficiency diseases. *Am J Digest Dis* 8 415-421, 1941
- 10 Kantor, J L. The roentgen diagnosis of idiopathic steatorrhea and allied conditions: practical value of the moulage sign. *Am J Roentgenol* 41 758-778 1939
- 11 Mackie, T T. Vitamin deficiencies and the small intestine. *J A M A* 117 910-912, 1941
- 12 Golden R. The small intestine in vitamin B deficiency. *J A M A* 117-913-917, 1941
- 13 Tyler A T. Study of the small bowel with special reference to avitaminosis. *Nebraska M J* 25-441-444, 1940
- 14 Riddle J W, Spies T D, and Hudson, N P. A note on the interrelationship of deficiency diseases and resistance to infection. *Proc Soc Exper Biol & Med* 45-361-364, 1940
- 15 Chapman O D, and Harris, A E. Oral lesions associated with dietary deficiencies in monkeys. *J Infectious Dis* 69 7-17, 1941
- 16 Mamon-Bahr, P H. Glossitis and vitamin B<sub>2</sub> complex in pellagra sprue and allied states. *Lancet* 2 317-320 356-359, 1940
- 17 Flom K O S, and Macchelli, T E. Studies of the B vitamins in the human subject. I. The intake of thiamine and its relation to other dietary constituents in food selected by the normal subject. *Am J M Sc* 202 502-512 1941

The first category, the unusual bone conditions, can probably be excluded, although at one time I made a list of forty-five different conditions that I have seen erroneously diagnosed as osteogenic sarcoma. The inflammatory conditions—tuberculosis, syphilis and osteomyelitis—must be considered. The joint was not involved. There was no evidence of tuberculosis elsewhere. The blood Hinton reaction was negative. Osteomyelitis is not suggested by either the physical examination or the laboratory findings. Metabolic disease may be well ruled out, for the blood chemical findings were normal, and there was no evidence of any disease of the other bones. The general physical examination was not remarkable, except that the patient was a rather slender man.

So far as metastatic tumors are concerned, there is no evidence of any tumor as a primary source of metastases. This condition had existed for three and a half years since the onset. The duration was one and a half years at the first admission, and the second admission was two and a half years later.

That brings us down to a primary tumor, either benign or malignant. A history of trauma is obtained in about 40 per cent of the cases of primary bone tumors. I think it is fairly safe to say that the tumor in this case was not malignant, for a malignant bone tumor would give some evidence of remote metastases three and a half years after onset. Giant-cell tumors often appear after injury in the humerus and in the knee. In the femur, they are apt to arise in the inner condyle; in the humerus, in the outer condyle. They originate in the medulla, cause bone destruction, extend to the cartilage, as this one did, without breaking through into the joint, and form an expanding bone tumor.

This x-ray film, I take it, is an early one. The outline of the periosteum is unbroken except at one point. There is some expansion in this other film. The gross description of the tumor removed at the first operation is certainly compatible with that of a giant-cell tumor.

These tumors appear in two forms: a currant-jelly-like, very vascular tissue, and fibrous tissue that is yellow in color, probably owing to deposits of hemosiderin and lipoid material. Following the first operation, the patient received x-ray treatment with no appreciable improvement, and he re-entered with essentially the same condition—a little more advanced. The second x-ray film shows bulging of the internal condyle down to the joint surface. I think that the limitation of motion was partly due to mechanical interference.

My diagnosis in this case is giant-cell tumor. Such tumors are cured at times by excision or

curettage, at times by radiation; in a study of a large series, about 30 per cent of the patients were not cured by either method and came eventually to amputation. About 7 per cent undergo malignant change. As I have seen these cases, the defect never fills up with normal bone, and if bone chips are placed in the cavity after curetting they are absorbed. My diagnosis is giant-cell tumor, running the course that many of them do.

DR. TRACY B. MALLORY: You would not be seriously worried over the possibility of malignant tumor?

DR. SIMMONS: No; I should not.

#### CLINICAL DIAGNOSIS

Giant-cell tumor, right elbow.

#### DR. SIMMONS'S DIAGNOSIS

Giant-cell tumor of humerus.

#### ANATOMICAL DIAGNOSIS

Giant-cell tumor of humerus.

#### PATHOLOGICAL DISCUSSION

DR. MALLORY: This lesion was once again curetted, and the gross material on this occasion was rather fibrous, with many yellow spots in it. It did not show any of the currant-jelly appearance. On microscopic examination, there are areas of quite characteristic giant-cell tumor. These are interspersed with areas of rather dense fibrosis in which a good many cholesterol-filled foam cells are found. There are a few trabeculae and osteoid material, but nothing that suggests malignant lesions. I suspect that the unusual degree of fibrosis could perhaps be attributed to the x-ray treatment that the patient had received off and on during this period.

DR. SIMMONS: I think that is the usual story—increased fibrosis following either curettage or x-ray treatment. The cavity never fills in with normal bone.

DR. GEORGE W. HOLMES: I should like to know, although I was present at the time this question of operation was discussed, just why they operated. I presume that it was to improve function, and I wonder if operation would improve function, because there is nothing in the lesion as I see it in the x-ray film to make me think of a malignant tumor; as a matter of fact, it really did improve somewhat under radiation. The outlines are sharp, it has not grown any in two years, and although it has not filled in with new bone, it is at least quiescent.

DR. MALLORY: The patient, who was a manual worker, had considerable limitation of function and found it difficult to work.

CASE RECORDS OF THE  
MASSACHUSETTS GENERAL HOSPITALANTE-MORTEM AND POST-MORTEM RECORDS AS USED  
IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

## CASE 28141

## PRESENTATION OF CASE

*First admission.* A thirty-five-year-old Russian butcher's helper was admitted to the hospital because of pain and disability in the right elbow for one month.

A year before entry, the right elbow was slammed by the door of an auto in which the patient was riding. There was considerable local pain at the time, but no swelling, discoloration or actual disability was noted. Since then, he had experienced occasional slight pain along the inner aspect of the elbow. In the month before entry, the pain tended to become severer, and he was unable to straighten the elbow fully. There were no constitutional symptoms.

On admission, the patient appeared thin and pallid. There was a smooth, rounded swelling over the internal condyle of the right humerus, enlarging this landmark to about twice its normal size. The skin overlying this mass was not attached, or otherwise altered. The mass was tender posteriorly only (in the region of the ulnar nerve). Extension was limited by about 20°, but other movements were normal. There was no evidence of interference with the ulnar nerve. The other extremities were normal, and the rest of the physical examination was negative.

The temperature, pulse, respirations and blood pressure were normal.

Examination of the blood showed a red-cell count of 4,800,000, and a white-cell count of 10,500 with 72 per cent polymorphonuclears. The blood calcium was 11.0 mg. and the phosphorus was 3.3 mg. per 100 cc.; the phosphatase was 3.4 Bodansky units. The blood Hinton reaction was negative. The total cholesterol was 114 mg. per 100 cc.

A roentgenogram showed a multilocular cystic area in the medial condyle of the right humerus. The bone appeared thickened anteriorly, without interruption of the cortex. The upper aspect of the facet of the trochlea seemed involved; this prevented complete extension of the elbow. The bone surrounding the lesion showed normal structure.

A roentgenogram of the left elbow was negative.

On the third hospital day, the medial aspect of the lower end of the right humerus was exposed and incised; this revealed a cavity from which portions of soft, friable yellowish tissue and of soft, pinkish currant-jelly-like tissue were readily curetted. The cavity was thoroughly curetted, not packed with bone chips, and closed by approximation of the muscle layers. Microscopic examination of the material removed showed a benign giant-cell tumor. The patient was discharged on the sixth postoperative day.

*Second admission* (two and a half years later). The patient was followed in the Tumor Clinic, receiving three courses of roentgen-ray therapy, of 800 r each. There was a gradual increase of flexion deformity to about 65°. The patient, however, was able to work as a mechanic, not lifting much weight. He was readmitted to the hospital because there was some question of increase in size of the residual mass in the elbow.

On re-examination, the general physical condition was normal. The left elbow was held in 65° flexion. Extension was limited to 70°, and flexion was limited to 120°. Full and painless pronation and supination were possible. There was a circumscribed, bony hard swelling over the medial humeral epicondyle, which was firmly attached to the bone and tender in some areas. There was full ulnar-nerve function. The axillary lymph nodes were not enlarged.

The temperature, pulse, respirations and blood pressure were normal.

Examination of the blood and urine was essentially as before. The blood calcium was 10.6 mg. and the phosphorus 3.2 mg. per 100 cc.; the phosphatase was 2.9 Bodansky units.

A roentgenogram of the chest showed some emphysema and pulmonary fibrosis, but no metastatic lesions. A roentgenogram of the right elbow showed no definite increase in the size of the lesion.

On the tenth hospital day, an operation was performed.

## DIFFERENTIAL DIAGNOSIS

DR. CHANNING C. SIMMONS: This man had some bone condition of the lower end of the humerus. There are many things to be considered, but roughly these bone conditions can be divided into five categories: unusual conditions, such as a coccidioidal infection and an echinococcal cyst, which I have never seen, although they occur in other parts of the country; an ordinary inflammatory lesion, such as tuberculosis, syphilis or osteomyelitis; metabolic disease, parathyroid disease or primary disease of bone, such as Paget's disease; metastatic tumors; and primary bone tumors, either malignant or benign.

18. Melnick, D., Robinson, W. D., and Field, H., Jr. Fate of thiamine in the digestive secretions. *J. Biol. Chem.* 138:49-61, 1941.
19. Borson, H. J. Clinical application of the thiochrome reaction in the study of thiamin (vitamin B<sub>1</sub>) deficiency. *Ann. Int. Med.* 14:1-27, 1940.
20. Williams, R. D., Mason, H. L., and Smith, B. F. Induced vitamin B<sub>1</sub> deficiency in human subjects. *Proc. Staff Meet., Mayo Clin.* 14:787-793, 1939.
21. Dyer, H. M., and Roe, J. H. The relation of nutrition to gastric function. III. The effect of vitamin B<sub>1</sub> deficiency. *Am. J. Digest. Dis.* 8:329-333, 1941.
22. Dick, M., and Hege, J. R., Jr. The effect of thiamin on the intestine of the B<sub>1</sub>-deficient rat. *Am. J. Physiol.* 132:636-639, 1941.
23. Crandall, L. A., Jr., Chesley, F. F., Hansen, D., and Dunbar, J. The relationship of the P-P factor to gastrointestinal motility. *Proc. Soc. Exper. Biol. & Med.* 41:472-474, 1939.
24. Nakamura, M., Hamada, C., and Oriuchi, H. Report of necropsy on pellagra. *Bull. Nat. M. A., Japan* 30:179, 1941.
25. Spies, T. D., Bean, W. B., and Ashe, W. F. A note on the use of vitamin B<sub>6</sub> in human nutrition. *J. A. M. A.* 112:2414, 1939.
26. Fouts, P. J., Helmer, O. M., and Lepkovsky, S. Factor II deficiency in dogs. *J. Nutrition* 19:393-400, 1940.
27. Spies, T. D., Bean, W. B., and Vilter, R. W. Adenylic acid in human nutrition. *Ann. Int. Med.* 13:1616-1618, 1940.
28. Martin, G. J., Thompson, M. R., and de Carvajal-Forero, J. The influence of inositol and other B complex factors upon the motility of the gastro-intestinal tract. *Am. J. Digest. Dis.* 8:290-295, 1941.
29. Elsom, K. O., Lewy, F. H., and Heublein, G. W. Clinical studies of experimental human vitamin B complex deficiency. *Am. J. M. Sc.* 200:757-764, 1940.
30. Spies, T. D., Grant, H. M., and Grant, J. M. Observations on the effectiveness of a yeast-peanut butter mixture in vitamin B complex deficiencies. *South. M. J.* 34:159-161, 1941.
31. Aballi, A. J., and Escobar Aces, A. Trastornos digestivos por carencias de factores del complejo vitamínico B. *Bol. Soc. cubana de pediat.* 12:91-135, 1940.
32. Sydenstricker, V. P. Syndrome of multiple vitamin deficiency. *Ann. Int. Med.* 15:45-51, 1941.
33. Bercovitz, Z. Recent advances in the treatment of chronic ulcerative colitis. *M. Clin. North America* 24:683-704, 1940.
34. Ludden, J. B., Flexner, J., and Wright, I. S. Studies on ascorbic acid deficiency in gastric diseases: incidence, diagnosis and treatment. *Am. J. Digest. Dis.* 8:249-252, 1941.
35. Field, H., Jr., Robinson, W. D., and Melnick, D. Vitamins in peptic ulcer. *Ann. Int. Med.* 14:588-592, 1940.
36. Ingalls, T. H., and Warren, H. A. Asymptomatic scurvy: its relation to wound healing and its incidence in patients with peptic ulcer. *New Eng. J. Med.* 217:443-446, 1937.
37. Minnich, V., Wright, S. T., Moore, C. V., and Spies, T. D. Whole blood and plasma ascorbic acid concentrations in patients with pellagra and associated deficiency diseases. *Proc. Soc. Exper. Biol. & Med.* 45:441-446, 1940.
38. Irvin, J. L., Kopala, J., and Johnston, C. G. The absorption of carotene from isolated intestinal loops. *Am. J. Physiol.* 132:202-210, 1941.
39. May, C. D., and McCreary, J. F. The absorption of vitamin A in celiac disease: interpretation of the vitamin A absorption test. *J. Pediat.* 18:200-209, 1941.
40. Ralli, E. P., Bauman, E., and Roberts, L. B. The plasma levels of vitamin A after the ingestion of standard doses: studies in normal subjects and patients with cirrhosis of the liver. *J. Clin. Investigation* 20:709-713, 1941.
41. Dyer, H. M., and Roe, J. H. The relation of nutrition to gastric function. IV. The effect of vitamin A deficiency. *Am. J. Digest. Dis.* 8:333-337, 1941.
42. Herrin, R. C. Gastric emptying time and acidity in avitaminosis A in dogs. *Am. J. Digest. Dis.* 7:164-166, 1940.
43. Földes, F., and Vajda, G. Effect of vitamin A on the secretion of gastric juice in deficient hydrochloric acid production. *Brit. M. J.* 1:317, 1941.
44. Seelig, S. F. Treatment of gastric ulcer with vitamin A. *Guy's Hosp. Rep.* 90:41-54, 1941.
45. Fridericia, L. S., Gudjonsson, S., Vimtrup, B., Clemmesen, S., and Clemmesen, J. Stomach lesions in rats kept on diets deficient in vitamin A. *Am. J. Cancer* 39:61-69, 1940.
46. Beck, S., and Peacock, P. R. Gastro-papillomatosis due to vitamin A deficiency induced by heated fats. *Brit. M. J.* 2:81-83, 1941.
47. Stryker, W. A., and Janota, M. Vitamin A deficiency and intestinal permeability to bacteria and toxin. *J. Infect. Dis.* 69:243-247, 1941.
48. Abels, J. C., Gorham, A. T., Pack, G. T., and Rhoads, C. P. Metabolic studies in patients with cancer of the gastro-intestinal tract. I. Plasma vitamin A levels in patients with malignant neoplastic disease, particularly of the gastro-intestinal tract. *J. Clin. Investigation* 20:749-764, 1941.
49. Albright, F., and Stewart, J. D. Hypovitaminosis of all fat-soluble vitamins due to steatorrhea. *New Eng. J. Med.* 223:239-241, 1940.
50. Warner, E. D., Spies, T. D., and Owen, C. A. Hypoproteinaemia and vitamin K in nutritional deficiency states. *South. M. J.* 34:161-163, 1941.

CASE RECORDS OF THE  
MASSACHUSETTS GENERAL HOSPITALANTE MORTEM AND POST MORTEM RECORDS AS USED  
IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

## CASE 28141

## PRESENTATION OF CASE

*First admission.* A thirty-five-year-old Russian butcher's helper was admitted to the hospital because of pain and disability in the right elbow for one month.

A year before entry, the right elbow was slammed by the door of an auto in which the patient was riding. There was considerable local pain at the time, but no swelling, discoloration or actual disability was noted. Since then, he had experienced occasional slight pain along the inner aspect of the elbow. In the month before entry, the pain tended to become severer, and he was unable to straighten the elbow fully. There were no constitutional symptoms.

On admission, the patient appeared thin and pallid. There was a smooth, rounded swelling over the internal condyle of the right humerus, enlarging this landmark to about twice its normal size. The skin overlying this mass was not at tached, or otherwise altered. The mass was tender posteriorly only (in the region of the ulnar nerve). Extension was limited by about 20°, but other movements were normal. There was no evidence of interference with the ulnar nerve. The other extremities were normal, and the rest of the physical examination was negative.

The temperature, pulse, respirations and blood pressure were normal.

Examination of the blood showed a red cell count of 4,800,000, and a white cell count of 10,500 with 72 per cent polymorphonuclears. The blood calcium was 11.0 mg., and the phosphorus was 3.3 mg per 100 cc.; the phosphatase was 3.4 Bodansky units. The blood Hinton reaction was negative. The total cholesterol was 114 mg. per 100 cc.

A roentgenogram showed a multilocular cystic area in the medial condyle of the right humerus. The bone appeared thickened anteriorly, without interruption of the cortex. The upper aspect of the facet of the trochlea seemed involved; this prevented complete extension of the elbow. The bone surrounding the lesion showed normal structure.

A roentgenogram of the left elbow was negative.

On the third hospital day, the medial aspect of the lower end of the right humerus was exposed and incised; this revealed a cavity from which portions of soft, friable yellowish tissue and of soft, pinkish currant-jelly like tissue were readily curetted. The cavity was thoroughly curetted, not packed with bone chips, and closed by approximation of the muscle layers. Microscopic examination of the material removed showed a benign giant-cell tumor. The patient was discharged on the sixth postoperative day.

*Second admission* (two and a half years later). The patient was followed in the Tumor Clinic, receiving three courses of roentgen ray therapy, of 800 r each. There was a gradual increase of flexion deformity to about 65°. The patient, however, was able to work as a mechanic, not lifting much weight. He was readmitted to the hospital because there was some question of increase in size of the residual mass in the elbow.

On re-examination, the general physical condition was normal. The left elbow was held in 65° flexion. Extension was limited to 70°, and flexion was limited to 120°. Full and painless pronation and supination were possible. There was a circumscribed, bony, hard swelling over the medial humeral epicondyle, which was firmly attached to the bone and tender in some areas. There was full ulnar nerve function. The axillary lymph nodes were not enlarged.

The temperature, pulse, respirations and blood pressure were normal.

Examination of the blood and urine was essentially as before. The blood calcium was 10.6 mg and the phosphorus 3.2 mg per 100 cc., the phosphatase was 2.9 Bodansky units.

A roentgenogram of the chest showed some emphysema and pulmonary fibrosis, but no metastatic lesions. A roentgenogram of the right elbow showed no definite increase in the size of the lesion.

On the tenth hospital day, an operation was performed.

## DIFFERENTIAL DIAGNOSIS

DR. CHANNING C. SIMMONS. This man had some bone condition of the lower end of the humerus. There are many things to be considered, but roughly these bone conditions can be divided into five categories: unusual conditions, such as a coccidioidal infection and an echinococcal cyst, which I have never seen, although they occur in other parts of the country; an ordinary inflammatory lesion, such as tuberculosis, syphilis or osteomyelitis; metabolic disease, such as Paget's disease; metastatic tumors; and primary bone tumors, either malignant or benign.

The first category, the unusual bone conditions, can probably be excluded, although at one time I made a list of forty-five different conditions that I have seen erroneously diagnosed as osteogenic sarcoma. The inflammatory conditions—tuberculosis, syphilis and osteomyelitis—must be considered. The joint was not involved. There was no evidence of tuberculosis elsewhere. The blood Hinton reaction was negative. Osteomyelitis is not suggested by either the physical examination or the laboratory findings. Metabolic disease may be well ruled out, for the blood chemical findings were normal, and there was no evidence of any disease of the other bones. The general physical examination was not remarkable, except that the patient was a rather slender man.

So far as metastatic tumors are concerned, there is no evidence of any tumor as a primary source of metastases. This condition had existed for three and a half years since the onset. The duration was one and a half years at the first admission, and the second admission was two and a half years later.

That brings us down to a primary tumor, either benign or malignant. A history of trauma is obtained in about 40 per cent of the cases of primary bone tumors. I think it is fairly safe to say that the tumor in this case was not malignant, for a malignant bone tumor would give some evidence of remote metastases three and a half years after onset. Giant-cell tumors often appear after injury in the humerus and in the knee. In the femur, they are apt to arise in the inner condyle; in the humerus, in the outer condyle. They originate in the medulla, cause bone destruction, extend to the cartilage, as this one did, without breaking through into the joint, and form an expanding bone tumor.

This x-ray film, I take it, is an early one. The outline of the periosteum is unbroken except at one point. There is some expansion in this other film. The gross description of the tumor removed at the first operation is certainly compatible with that of a giant-cell tumor.

These tumors appear in two forms: a currant-jelly-like, very vascular tissue, and fibrous tissue that is yellow in color, probably owing to deposits of hemosiderin and lipid material. Following the first operation, the patient received x-ray treatment with no appreciable improvement, and he re-entered with essentially the same condition—a little more advanced. The second x-ray film shows bulging of the internal condyle down to the joint surface. I think that the limitation of motion was partly due to mechanical interference.

My diagnosis in this case is giant-cell tumor. Such tumors are cured at times by excision or

curettage, at times by radiation; in a study of a large series, about 30 per cent of the patients were not cured by either method and came eventually to amputation. About 7 per cent undergo malignant change. As I have seen these cases, the defect never fills up with normal bone, and if bone chips are placed in the cavity after curetting they are absorbed. My diagnosis is giant-cell tumor, running the course that many of them do.

DR. TRACY B. MALLORY: You would not be seriously worried over the possibility of malignant tumor?

DR. SIMMONS: No; I should not.

#### CLINICAL DIAGNOSIS

Giant-cell tumor, right elbow.

#### DR. SIMMONS'S DIAGNOSIS

Giant-cell tumor of humerus.

#### ANATOMICAL DIAGNOSIS

Giant-cell tumor of humerus.

#### PATHOLOGICAL DISCUSSION

DR. MALLORY: This lesion was once again curetted, and the gross material on this occasion was rather fibrous, with many yellow spots in it. It did not show any of the currant-jelly appearance. On microscopic examination, there are areas of quite characteristic giant-cell tumor. These are interspersed with areas of rather dense fibrosis in which a good many cholesterol-filled foam cells are found. There are a few trabeculae and osteoid material, but nothing that suggests malignant lesions. I suspect that the unusual degree of fibrosis could perhaps be attributed to the x-ray treatment that the patient had received off and on during this period.

DR. SIMMONS: I think that is the usual story—increase in fibrosis following either curettage or x-ray treatment. The cavity never fills in with normal bone.

DR. GEORGE W. HOLMES: I should like to know, although I was present at the time this question of operation was discussed, just why they operated. I presume that it was to improve function, and I wonder if operation would improve function, because there is nothing in the lesion as I see it in the x-ray film to make me think of a malignant tumor; as a matter of fact, it really did improve somewhat under radiation. The outlines are sharp, it has not grown any in two years, and although it has not filled in with new bone, it is at least quiescent.

DR. MALLORY: The patient, who was a manual worker, had considerable limitation of function and found it difficult to work.

DR. GEORGE W. VAN GORDER: After considerable discussion in the Tumor Clinic and in the Orthopedic Staff, it was decided that the wisest operative procedure to carry out on this patient's arm was excision of the tumor, in addition to an arthrodesis of the elbow joint, allowing the radial head to remain free to rotate in a normal way on the remaining external condyle of the humerus.

The reason that a movable elbow joint was not considered advisable was that the tumor occupied too great a portion of the articular surface to allow for normal motion or stability after its excision. In other words, more than half the articular surface of the lower end of the humerus would have had to be sacrificed, and this would have resulted in a useless joint. An alternative was to perform a complete excision of the lower end of the humerus, but this would also have involved too great a portion of bone to permit any future stability or strength in the joint. Since this patient is the father of a family and has to work, and since he could not do his work with a flail elbow, it was decided that a firm ankylosed joint in an optimal position of election would be the most satisfactory answer to his problem from an economic and social point of view. The patient was asked about the type of work that he performed and the angle at which his elbow was most useful in carrying on his job, the idea being that if the joint were solidly fused at the proper angle, it would later be of the greatest service to him. These matters were all considered before the operative procedure was carried out.

In the surgical procedure itself, the tumor was completely excised, and following excision, the cartilaginous surface of the ulna and its adjacent humeral articular surface were removed, after which a long vitallium bone plate, which had previously been bent at the proper angle, was applied to the posterior aspect of the joint, with three screws to hold it to the lower end of the humerus and with three screws to the shaft of the ulna.

Following application of this plate, the elbow joint seemed to be firm and in its proper position, and the upper end of the radius was not interfered with at all, so that full rotation of the forearm remained undisturbed. Two drill holes, each 6 mm. in diameter, were then made through the external condyle of the humerus across the joint line into the ulna, and into these drill holes two tibial bone grafts were driven, which acted as dowels, anchoring the two bones together. A third bone graft was placed between the humerus and ulna in another direction, avoiding the radiohumeral articulation.

The wound was then closed, in the hope that solid union would take place between the ulna and external condyle of the humerus and that ro-

tation motion would be preserved for the forearm. Should this result be obtained, the patient will be able to continue his job or at least do heavy work with a very useful arm.

## CASE 28142

### PRESENTATION OF CASE

A thirty-year-old housewife was admitted to the hospital because of a mass in the upper jaw.

The patient was well until six months before entry, when, in the fifth month of an otherwise normal fifth pregnancy, she noted a slightly painful gray, purulent swelling on the upper jaw, where a tooth had been extracted several years previously. Two weeks later, a smooth, firm, slightly painful lump appeared at the same site on the buccal side of the jaw. It grew rapidly for a month, and then it was excised in another hospital. Following this, there was a recurrence of the lesion, with spread over a larger area of the jaw. The mass was re-excised in the other hospital on two subsequent occasions. The pathological diagnosis each time was epulis. Following the last excision, two months before entry, the mass became so large that the patient had trouble in closing her mouth, and in chewing her food. At times, there was a dull ache in the jaw, with occasional radiation to the neck. There was no pain elsewhere. The pregnancy terminated in normal delivery two weeks before entry.

The past history was noncontributory. Four earlier pregnancies had resulted in two miscarriages and two living children. The family history was irrelevant.

On admission, the patient appeared well developed and nourished. The left cheek was distended by a firm mass, extending from the midline near the nose back to within 2 cm. of the ear, and from below the eye down to the mandible. The left nostril was not obstructed. Just under the lip, the lower edge of the mass was denuded of epithelium, appearing yellow brown with spots of old blood. Within the mouth, the swelling approached the midline of the hard palate, irregularly. The buccal aspect of the left maxilla was occupied entirely by the mass. The swelling was moderately tender. Both tonsils were enlarged, and an apparent lymph node was palpable, in the left supraclavicular region. The spleen was questionably palpable, and there was moderate suprapubic tenderness. Pelvic examination showed normal puerperal changes. General physical examination was otherwise negative.

The blood pressure, temperature, pulse and respirations were essentially normal.

Examination of the blood and urine was essentially negative. The blood calcium was 10.4 mg.



and the phosphorus 3.4 mg. per 100 cc., and the phosphatase was 3.5 Bodansky units.

Roentgenograms of the jaw showed an area of destruction in the left maxilla extending from the spinous process and the midline back to within 0.5 cm. of the posterior margin. The involved bone appeared moth-eaten and almost completely destroyed. The apexes of the bicuspids, cuspids and lateral incisor were involved. A large soft-tissue mass extended beneath the lip and cheek, including several fine bone spicules. There was an apparent bulge into the left maxillary antrum. This cavity was enlarged in all directions, and its wall appeared broken through in several places. A roentgenogram of the chest was negative.

A biopsy of the mass was taken on the second hospital day, and a week later an operation was performed.

#### DIFFERENTIAL DIAGNOSIS

DR. HAROLD G. TOBEY: This is a rather short history of what apparently was a malignant tumor. We can probably rule out acute or chronic infection of the sinuses. The entire history was too short for any chronic infection, except possibly an osteomyelitis, which might develop as quickly as this, but probably would not. The only specific infection we must consider is the possibility brought up by the yellow-brown spots, particularly the yellow, which might suggest actinomycosis. There is no bacteriologic report; presumably, that was thought of and ruled out. Here again, six months is a rather short time for such a rapid spread, even of actinomycosis. So that we are brought down to the possibility of a malignant growth.

The alveolar process and the sinuses are subject to the usual malignant growths, carcinoma and sarcoma, and at times some of the lymphomas. It is significant that a few years previously a tooth had been extracted, and the tumor presumably occurred at the site of this tooth. The tumor was removed, and a diagnosis of epulis was made. It is possible that the diagnosis was incorrect. The ordinary epulis presents a picture similar to that of a benign giant-cell tumor of bone, but sarcomatous "degeneration" of the latter is conceivable. The recurrence happened in exactly the same place where the mass had been removed. So far as epithelioma is concerned, it is usually much more slowly progressing. It may start inside the antrum, possibly where the tooth was extracted. The fact that both tonsils were enlarged makes me think of the possibility of lymphoma, but there was practically no adenopathy. One lymph node was palpated in the left supraclavicular region, but nothing is said about palpation of lymph nodes elsewhere.

May we see the x-ray films?

DR. GEORGE W. HOLMES: These two small films show the extent and character of the lesion better than any of the others. It is quite large, moderately dense, and, what is most important, shows spicules of bone within the tumor substance. It has partially destroyed the antrum, and there is bulging of the bone, which is a little unusual. A rapidly growing malignant tumor does not as a rule cause bulging, but simply destroys the walls. This has done both. It is essential to know whether the floor of the orbit is destroyed or not. We thought it was at least infiltrated by this growth and partially destroyed. This tumor has some of the characteristics of benign tumor and some of the characteristics of a malignant tumor. I think it would be fair to say that it would be very difficult to explain the infiltration of bone and the presence of spicules in a benign lesion.

DR. TOBEY: The benign lesions usually expand the bone, and the bone is absorbed by pressure.

There is a tumor called a "pregnancy tumor," which I have never seen and know nothing about, but it does occur about the alveolar processes.

There are other conditions that might be considered; one of them is mucocoele of the sinus, which is more common in the frontal sinus, with destruction of the bone and smooth surfaces, but this is altogether too rapidly growing for a mucocoele. In the absence of any acute infection and in view of the involvement and active destruction of the bone, I should say that this tumor was probably an osteogenic sarcoma.

DR. CHANNING C. SIMMONS: I saw this woman, and the question of whether this was a pregnancy tumor arose. I reviewed two articles on the subject, and the largest pregnancy tumor reported was 1.5 cm. in diameter. I also talked with some of the dental surgeons about pregnancy tumors of the mouth, and was told that a shaggy appearance of the mucous membrane over the alveolar process was not uncommon. This tissue is very vascular, but it usually disappears after delivery. I have also seen angiomas about the mouth and elsewhere that increased in size during pregnancy and went down afterward. There is apparently some metabolic disturbance that makes them grow. This particular tumor was a new growth of either sarcomatous or possibly adamantinomatous type; but it was very rapidly growing for the latter. The other thing I might say is that a tumor with a histologic picture such as this, if it occurred in the long bone, would probably cause death with metastasis, but in the jaw such tumors do not often metastasize.

A PHYSICIAN: What about ossifying fibromas?

DR. SIMMONS: I have never seen one. I have

seen diffuse fibromas of the upper jaw, where the antrum is thickened and the whole upper jaw transformed into rather soft ossifying tissue. They apparently arise from the inner process of the superior maxilla and fill the antrum.

DR. HOLMES: They cause a much denser shadow than this one did, and completely obliterate the entire area of the sinus.

DR. SIMMONS: They are slowly growing tumors and occur in patients of about ten to fifteen years of age.

DR. LANGDON PARSONS: The last biopsy taken from the tumor itself was reported as ossifying fibroma. When the entire maxilla was removed and the specimen in the pathologist's hand, the report was still ossifying fibroma. So far as the orbital floor was concerned, it was completely destroyed. This tumor had definitely grown under observation in the week that the patient spent on the wards.

DR. SIMMONS: Was it encapsulated?

DR. PARSONS: Yes, except for the part that had broken into the orbit.

DR. TOBEY: Is that not quite fast for sarcoma? It suggests a rapidly growing lymphoma.

DR. SIMMONS: Do you think that the pregnancy had anything to do with the rapidity of growth?

DR. TRACY B. MALLORY: I do not know the answer to that. One suspects it, of course. Pregnancy can influence the growth of a variety of tumors.

#### CLINICAL DIAGNOSIS

Ossifying fibroma of maxilla.

#### DR. TOBEY'S DIAGNOSIS

Osteogenic sarcoma of maxilla.

#### ANATOMICAL DIAGNOSIS

Osteogenic sarcoma of maxilla.

#### PATHOLOGICAL DISCUSSION

DR. MALLORY: The early biopsies on this tumor were all rather inadequate, and for that reason the diagnosis was not made sooner. The final specimen showed undifferentiated, anaplastic cells embedded in osteoid tissue, and on a histologic basis one could not call it anything but an osteogenic sarcoma.

What the outlook is I do not know. As Dr. Simmons said, tumors in this area often behave more benignly than their histologic characteristics lead one to predict, so that it is possible that the patient has been cured and will not have a metastasis. Had this tumor occurred in a long bone, I should not hold out any hope whatever.

DR. HOLMES: Did the patient have any radiation?

DR. PARSONS: She had had some before she came here. We were never able to find out how much.

DR. MALLORY: The immediate results of operation were excellent. It was possible to excise all the visible tumor, and in spite of the fact that there is no floor to the orbit, the eye is not sagging and the vision is good.

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established in 1828

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND  
PUBLISHED UNDER THE JURISDICTION OF THE  
COMMITTEE ON PUBLICATIONS

Official Organ of  
THE MASSACHUSETTS MEDICAL SOCIETY  
and  
THE NEW HAMPSHIRE MEDICAL SOCIETY

## EDITORIAL BOARD

Joseph Garland, M.D.	Stephen Rushmore, M.D.
William B. Breed, M.D.	Henry R. Viets, M.D.
George R. Minot, M.D.	Robert M. Green, M.D.
Frank H. Lahey, M.D.	Charles C. Lund, M.D.
Shields Warren, M.D.	John F. Fulton, M.D.
George L. Tobey, Jr., M.D.	A. Warren Stearns, M.D.
C. Guy Lane, M.D.	Dwight O'Hara, M.D.
William A. Rogers, M.D.	Chester S. Keefer, M.D.

## ASSOCIATE EDITORS

Thomas H. Lanman, M.D.	Donald Munro, M.D.
Henry Jackson, Jr., M.D.	

Walter P. Bowers, M.D., EDITOR EMERITUS  
Robert N. Nye, M.D., MANAGING EDITOR  
Clara D. Davies, ASSISTANT EDITOR

**SUBSCRIPTION TERMS:** \$6.00 per year in advance, postage paid, for the United States (medical students, \$3.50 per year); Canada, \$7.04 per year, Boston funds; \$8.52 per year for all foreign countries belonging to the Postal Union.

MATERIAL for early publication should be received not later than noon on Friday.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston, Massachusetts.

## EARLY RISING AFTER OPERATIONS

THE supposed necessity of keeping patients in bed for a more or less arbitrary minimum period of about a week and in the hospital for ten days after many of the less severe major operations not associated with prostrating illness has recently been questioned in several countries.<sup>1-4</sup> Leithäuser and Bergo's<sup>1</sup> study of this subject presents data on 370 cases subjected to appendectomy and on 66 cases having had other operations. The study appears to prove that nothing harmful is likely to happen to these patients if they get out of bed on the day after operation. The authors even claim that this method of postoperative care gives excellent results, since there was not a single case with

pulmonary complications, dehiscence, postoperative hernia, thrombophlebitis or death. Their treatment really consists of a logical extension of certain ideas concerning the prevention of pulmonary complications that have recently been enthusiastically adopted by certain surgeons, although first proved valuable twenty-five years ago.<sup>5</sup> The late Dr. E. Amory Codman, of Boston, once expressed the opinion that the time would come "when interval and prophylactic appendectomy would be performed through a McBurney incision under local procaine anesthesia in the surgeon's office, and the patient would be allowed to go home a few hours later."<sup>6</sup>

The details of Leithäuser and Bergo's<sup>1</sup> treatment are as follows:

After operation the patients were turned frequently in bed and were instructed to be active and to take deep breathing exercises at regular intervals. On the first postoperative day, provided conditions were satisfactory, they were assisted in sitting on the edge of the bed [after assuming the right lateral position] and then in standing beside the bed for deep breathing exercises. [This consumed only a few moments.] While in each position they were instructed to take several deep inhalations and were urged to cough. This procedure seldom failed promptly to clear the lungs of accumulations of mucus. After this was accomplished they were permitted to walk about the room and to sit in a chair for a few moments, and then they returned to bed. On returning they sat on the edge of the bed and reclined on the right shoulder. These sitting-up and ambulatory exercises were always first carried out under the supervision of one of us. Such exercises were then repeated during the first postoperative day with the assistance of a nurse, and thereafter the patients were encouraged to increase their activities voluntarily. They left the hospital by automobile. . . .

It is unfortunate that no statement is made regarding the time of determination of the presence or absence of postoperative hernia, since many surgeons are skeptical of such findings unless systematic search has been made at least six months after operation. It goes without saying that the authors' method of suturing wounds, in which No. 0 chromic catgut and steel wire or nylon were employed, was eminently satisfactory.

The average duration of confinement to bed of the appendectomy patients was 1.5 days: 75 per

cent of them arose on the first day, 12 per cent on the second, and 8 per cent on the third. The average stay in the hospital was 2.3 days: 37 per cent of the patients left on the first day, 32 per cent on the second, 14 per cent on the third, and 10 per cent on the fourth. These figures are extremely interesting and significant, and bear comparison with those of similar cases treated according to more orthodox methods. For example, in the months of March and September, 1941, of 39 ward and 267 semiprivate patients who held policies issued by the Massachusetts Hospital Service (Blue Cross) and who were operated on for appendicitis (all types), the total stay in the hospital averaged 10.6 and 12.5 days, respectively.<sup>7</sup> Furthermore, according to the statements of six prominent Boston surgeons,<sup>8</sup> the average time for the earliest getting-up of their private and ward patients with simple appendectomies is 5.7 days, with an average time of 6.7 days for all cases, and the average time for the earliest discharge from the hospital is 8.3 days, with a slightly higher average for all cases.

From these data, it is evident that an appreciable difference exists between the times of the cases treated by Leithauser and Bergo and those given the usual postoperative care. One might argue that patients should be allowed to get up one or two days earlier without further ado, thereby saving that much time in the hospital. Many believe, however, that such a procedure might not be so safe as really early rising, because it is likely that most wounds are stronger on the first and second days after operation than they are for the following week, owing to the well-known "lag period" in healing and the gradual weakening of certain suture material. In any event, it is possible that great savings in complications, let alone costs, would arise following the general adoption of the early-rising technic. It would be well worth while for others to experiment along this line.

#### REFERENCES

1. Leithauser, D. J., and Bergo, H. L. Early rising and ambulatory activity after operation means of preventing complications. *Arch Surg* 42:1086-1093, 1941.
2. Mermingaz, K. Die Appendektomie ohne folrende Muskelnaht. *Zentralbl f. Chir* 60:553, 1933.

3. Mikhlin, M. V. Early rising after appendectomy in acute period. *Levinich Khir* 40:231-235, 1935.
4. Khromov, B. M. Value of early rising after operation in prevention of postoperative pulmonary complications. *Soviet Khir* 9:389-397, 1936.
5. Pool, E. H. Systematic exercises in postoperative treatment. *J. A. M. A.* 60:1202-1204, 1913.
6. Stewart, J. D. Surgical care and operative technic. *New Eng J Med.* 225:620-625, 1941.
7. Cabot, R. C. Personal communication.
8. Personal communications.

#### THE CONTROL OF CANCER

IN times when practically the total effort of this country is aimed toward a destruction of the young and healthy men of other countries, it seems almost useless to attempt to maintain interest in cancer control. However, regardless of war and sudden death, cancer will continue to make its inroads, sometimes taking the most useful and productive minds from the community. Because of the character of the disease itself and its high rate of mortality, there are few maladies that can compete with it from the standpoint of economic loss. Hence, even in these days, the medical profession, with its continuous contacts with the victims of cancer, should keep in mind the menace of this disease and the value of its control. In addition to their heavy emergency obligations, physicians must not forget this ever-present threat to life and happiness. Of special importance are the detection and cure of early cases of cancer, to lessen the burden on the hospital facilities of the community that is made all too heavy by the advanced or terminal cases of the disease.

In the past, notable gains in cancer control have been made in Massachusetts, and the American Society for the Control of Cancer is doing much throughout the country to check the advancing mortality from this disease. Ignorance, fear and procrastination should not be permitted to turn curable cases of cancer into hopeless ones.

For the past few years, April has been designated as "Cancer Month" by proclamation of the President. In the pressure of world events, this designation seems about as futile as a last year's newspaper, but just as the lesson to be learned from last year's newspaper was there for all to see, the knowledge of what should be done to control cancer is almost as plainly written, and fully as easily forgotten.

## MEDICAL EPONYM

## NEISSER'S DIPLOCOCCUS

Albert Neisser (1855-1916), when he was an assistant in the dermatologic clinic at the University of Breslau, published his paper "Über eine der Gonorrhoe eigenthümliche Micrococcusform [A Form of Micrococcus Peculiar to Gonorrhea]" in the *Centralblatt für die medicinischen Wissenschaften* (17:497-500, 1879). A portion of the translation follows:

If gonorrheal pus is spread as thinly as possible on a glass slide after Koch's method, allowed to dry and stained by simply flooding with an aqueous solution of methyl violet, and dried again, examination of the preparation under high power with the light cut down as little as possible will show at first glance, in addition to the dark violet-blue and variously shaped nuclei of the pus cells (the protoplasm of which is also stained, but only faintly), a number of more or less abundant clumps of micrococci. These have a quite characteristic and promptly recognizable typical form. . . . Nearly always two micrococci are seen lying close together—so closely that they give the impression of a single organism which is roll-shaped or biscuit-shaped, resembling a figure eight.

R. W. B.

## MASSACHUSETTS MEDICAL SOCIETY

## COMMITTEE ON MATERNAL WELFARE

CASE HISTORY: CURETTAGE CAUSING  
PERFORATION OF THE UTERUS AND FATAL SEPSIS

Because of continued bleeding, a thirty-year-old primipara entered the hospital twenty-five days after the delivery of a stillborn baby. The past history was irrelevant. There was no evidence of previous illness. The heart, lungs and blood pressure were said to have been normal. There is no record of a blood examination at the time of admission, and no description of the patient's labor. On admission, a curettage was performed, and in the process the uterus was perforated at the junction of the internal os and the anterior wall. According to the record, no intestine was brought down or injured. As soon as it was appreciated that the uterus had been perforated, the operation was stopped, and a gauze strip was placed in the perforation. The patient ran a septic course for three weeks. At the end of this time, the temperature reached normal and remained so for a week, when transfusion was performed. There is no evidence in the record of the blood picture that justified this transfusion. The transfusion itself was followed by a slight febrile reaction but the patient was sent home the following day. She remained in bed at home for

a week, re-entered the hospital, and died of fulminating septicemia in less than twenty-four hours.

*Comment.* It is unfortunate that the record does not give more specific details of the delivery and subsequent convalescence. It is quite possible that the continued bleeding was caused by some small piece of placenta, which may have been adherent and may have had to be removed manually at the time of delivery. It is probable that this patient had fever before she entered the hospital; in that event, invasion of the uterus, unless the hemorrhage was profuse, was contraindicated. The fever, which is reported to have followed the curettage, in all probability meant that the uterus was harboring a low-grade infection at the time of entry and that the operative procedure of curettage broke down Nature's defensive wall and resulted in a spread of infection that demonstrated itself in the fever, which lasted for three weeks. It is quite probable that the perforation of the uterus was an incident and had nothing to do with the final outcome. During the week that the patient was home in bed, the history does not tell whether or not the temperature was normal, but it probably was not. The transfusion must have been given because of a low red-cell count and possibly for the purpose of stimulating recovery from the anemia associated with infection. In itself, the transfusion could not have precipitated the ultimate septicemia.

This case illustrates primarily the seriousness of curetting any patient with a temperature following childbirth as well as, of course, following abortion. The uterus in such a case should be left absolutely alone except in the presence of frank hemorrhage, when intrauterine manipulation should be conducted in the gentlest fashion, preferably with the finger.

## COMMITTEE TO REVISE THE BY-LAWS

The following is the revised copy of the by-laws of the Society that will be presented by the Committee to Revise the By-laws to the Council for approval at its special meeting on April 15.

J. HARPER BLAISDELL, *Chairman*  
CARL BEARSE, *Secretary*  
JOHN FALLON  
HAROLD R. KURTH

\* \* \*

## CHAPTER I

## FELLOWSHIP

*Section 1.* Applicants for fellowship in the Massachusetts Medical Society are required to satisfy the censors that they are not less than twenty-one years of age; that they are of sound mind and of good

5 character, that they have a Baccalaureate or Do-  
 10 torate of Medicine from a medical school approved  
 by the Council, or have received the approval of the  
 Committee on Membership, that they have received  
 a license to practice medicine within the United  
 States or its territories, that they do not practice  
 medicine in a manner contrary to the code of ethics  
 of the Society, that they have made application  
 according to the provisions of Chapter V, and  
 15 that they have paid the examination fee of three  
 dollars

They shall appear personally before the censors  
 and satisfy them that the above requirements are  
 fulfilled

*Section 2* Applicants found to be so qualified  
 shall, on paying the assessment for the current fiscal  
 year (except as hereafter provided in Section 6  
 5 of this chapter) and subscribing to the by laws and  
 code of ethics, all within two weeks from the date  
 of their examinations, be approved by the censors

They furthermore shall, on confirmation by the  
 president and by the secretary of the Society, be  
 admitted fellows of the Society and shall receive  
 10 certificates of fellowship in testimony thereof signed  
 by the President and by the Secretary

*Section 3* Fellows having a legal residence in  
 Massachusetts shall be known as resident fellows  
 all others, as nonresident fellows

Nonresident fellows shall receive the official pub-  
 5 lications of the Society and may attend Society  
 meetings, but may not vote, hold office or receive  
 protection under the medical defense act of the  
 Society

*Section 4* Honorary fellowship may be conferred  
 on distinguished members of the medical profes-  
 sion

Associate fellowship may be conferred on eminent  
 5 workers in the allied sciences

Such fellowships may be conferred by a two-thirds  
 vote of the Council at a stated meeting, provided  
 10 written nominations therefor have been submitted  
 by two or more fellows at a previous stated meet-  
 ing and have been approved by the Committee on  
 Membership

Honorary and associate fellows may attend and  
 address meetings of the Society, but shall not be  
 15 accorded other rights or privileges, or be subject  
 to assessment

*Section 5* Fellows who are sixty five years of age  
 or older whose assessments have been paid or re-  
 mitted may, by vote of the Executive Committee,  
 5 acting on recommendation of the Committee on  
 Membership, become retired fellows

They shall be in good standing, and may attend  
 and address meetings of the Society, but shall not  
 be accorded other rights or privileges, except that,  
 10 on request annually, they shall receive the publica-  
 tions of the Society

They shall not be subject to assessment  
 Applications for retirement shall be addressed to  
 the Executive Committee and sent to the Treasurer

Retired fellows may, on their own request, be  
 15 restored to active fellowship by the Executive Com-  
 mittee.

*Section 6* Fellows shall be assessed such sums  
 as are voted by the Council, and such additional  
 sums as are voted by the district societies for their  
 own use

5 The fiscal year shall begin on the first day of  
 January Assessments shall be paid in advance  
 The first assessment paid by a fellow admitted to  
 the Society following the December examinations  
 shall cover his dues for the succeeding fiscal year  
 10 and shall be the amount fixed for that year

Assessments may be remitted by the Executive  
 • Committee on recommendation by the Committee  
 on Membership

Whenever a fellow owing more than one annual  
 15 assessment pays in part, the payment or payments  
 so made shall be considered as on the assessment  
 or assessments longest due and for no others

*Section 7* Resignations shall be submitted in  
 writing to the Treasurer, who shall deliver them  
 to the Committee on Membership

This committee shall submit them with recom-  
 5 mendations to the Executive Committee for action

Resignations shall be accepted only from fellows  
 whose assessments have been remitted or paid in full

*Section 8* Fellows who despite notification by  
 registered letter from the Treasurer, have not paid  
 assessments for two years, or who, despite notifica-  
 5 tion by registered letter from a district treasurer,  
 have not paid the assessments of their district society  
 for two years, shall be deprived of the privileges  
 of fellowship by the Executive Committee, acting  
 on a report of the Committee on Membership,  
 unless otherwise ordered

*Section 9* Fellows who have been convicted in  
 a court of law of a crime involving moral turpitude  
 or who have been guilty of attempts to harm the  
 Society or to injure its usefulness, of advertising  
 5 nostrums for sale or otherwise offering them to the  
 public, or professing to cure disease by secret meth-  
 ods, of gross violations of these by laws, of the code  
 of ethics of the Society or of the American Medical  
 Association, of presenting false certificates or false  
 10 statements of character or of educational require-  
 ments of accepting rebates on prescriptions or ap-  
 pliances, or of any other conduct unbecoming a  
 physician, may be expelled from the Society or  
 otherwise disciplined as provided in Chapter VIII,  
 15 Section 9

A fellow who has been deprived of his license  
 to practice medicine in the Commonwealth shall  
 automatically cease to be a fellow of the Society

*Section 10* Former fellows who desire to be  
 readmitted following retirement, resignation not  
 requested by the Committee on Ethics and Disci-  
 5 pline, or deprivation of fellowship for arrears shall  
 make application in writing addressed to the Execu-  
 tive Committee and sent to the Secretary

Such applications shall be referred for investiga-  
 10 tion to the board of membership of the district  
 society concerned, which shall report with recom-  
 mendations to the Committee on Membership

This committee shall report with recommenda-  
 tions to the Executive Committee

The Executive Committee may readmit former  
 fellows so recommended

*Section 11* Committees living under considera-  
 tion the applications of former fellows (a) whose  
 resignations have been requested by the Committee  
 on Ethics and Discipline or (b) who have been

- 5 deprived of fellowship under the terms of Section 9 shall consult with the Committee on Ethics and Discipline before reporting their recommendations to the Council.

## CHAPTER II

### MEETINGS OF THE SOCIETY

*Section 1.* The annual meeting of the Society shall be held in Boston, on the second Wednesday of June, unless otherwise ordered by the Council.

- 5 The order of business shall be: (1) reading of the record of the last annual meeting; (2) report by the Secretary of changes in membership during the year; (3) report by the President on the state of the Society; (4) such other business as may lawfully come before the meeting; (5) annual oration.

*Section 2.* Special meetings of the Society may be called by the President, or by vote of the Council, and shall be called on written request by ten councilors or one hundred fellows.

*Section 3.* The deliberations of the Society shall be governed by parliamentary usage as interpreted by *Roberts' Rules of Order*, when not in conflict with the by-laws of the Society.

- 5 One hundred fellows shall constitute a quorum.

## CHAPTER III

### DISTRICT SOCIETIES

*Section 1.* The boundaries of district societies may be changed, and new districts may be established, by the Council.

*Section 2.* The membership of each district society shall consist only of such fellows, whether active or retired, as have legal residences within the boundaries of the district, except in cases decided otherwise by vote of the Executive Committee.

- 5 *Section 3.* Any fellow wishing to transfer membership from one district society to another without a change of legal residence must so petition the Committee on Membership in writing, stating his reasons therefor.

The Committee on Membership shall report, after consultation with the officers of the two districts concerned, its recommendations to the Executive Committee for action.

*Section 4.* Each district society may adopt by-laws and regulations for the government of its own affairs and levy assessments, provided such by-laws and regulations are not in conflict with those of the Society.

*Section 5.* Each district society shall hold its annual meeting between the fifteenth day of April and the fifteenth day of May.

- 5 Each district society at this meeting shall elect by ballot from its active fellows: a president, who shall be *ex officio*, a vice-president of the Society; a vice-president; a secretary; a treasurer; councilors as below specified; four censors; a supervising censor; a commissioner of trial; a member of the Committee on Public Relations; a member of the Committee on Legislation; a member and alternate member of the Committee on Nominations.

- 15 Councilors shall be elected in number equal to one for every twenty active and retired fellows and a majority fraction thereof, as of the first day of January preceding.

Only councilors shall be eligible as supervising censors and members of the Committee on Public Relations and the Committee on Legislation.

- 20 Only councilors who have held this office for at least one year shall be eligible as members of and alternates to the Committee on Nominations. Members of and alternates to the Committee on Nominations shall not serve for more than five consecutive years and shall not be eligible for re-election for three years thereafter.

- 25 Only fellows who have been members of the Society for at least ten years shall be eligible as censors or supervising censors. The term of the supervising censors shall be five years. They shall not immediately succeed themselves. All supervising censors shall have been censors previously.

- 30 Councilors, censors, supervising censors, members of the Committee on Public Relations, members of the Committee on Legislation, members of the Committee on Nominations, and commissioners of trial shall take office at the close of the next annual meeting of the Society.

- 40 The councilors of each district society shall meet on call by the secretary at or as soon as possible after the annual meeting of the district society and elect two of their number to serve as member and alternate of the Executive Committee, in accordance with Chapter VII, Section 2.

- 45 Members of and alternates to the Executive Committee shall serve for three years and shall not be eligible for re-election for three years thereafter.

- 50 The term of office of the alternate shall be concurrent with the term for which the member was elected.

Vacancies that occur during the term of office of such member or alternate shall be filled promptly by vote of the councilors of the district concerned *ad interim*.

*Section 6.* The secretary of each district society promptly after its annual meeting, shall report on appropriate forms, to the Secretary the names and residences of fellows elected, as provided in Chapter III, Section 5.

He shall promptly notify the Secretary, on the required form, of deaths of fellows in his district.

He shall also perform such duties as are defined in Chapter V.

- 10 He shall call, at or as soon as possible after the annual meeting of the district society and before the annual meeting of the Society, meetings of the district councilors to elect the member and alternate of the Executive Committee, and shall send to the Secretary the names of the member and alternate chosen.

He shall see that a new member or alternate is chosen in a similar manner to fill a vacancy as it occurs, as provided in Section 5.

*Section 7.* The treasurer of each district society shall collect the assessments of his district.

- 5 He shall furnish a list of fellows two years in arrears to the Committee on Membership for action as provided in Chapter I, Section 8.

## CHAPTER IV

### THE COUNCIL

*Section 1.* The Council shall consist of councilors chosen by the district societies, the president, ex-presidents, president-elect, vice-president, vice-presidents *ex officio*, secretary, treasurer, and assistant.

5 treasurer of the Society the secretaries of the district societies and the chairmen of all standing committees

10 The Council each year shall hold three stated meetings in Boston, unless otherwise ordered by the Council. The annual meeting shall be held on the day next preceding the annual meeting of the Society. A stated meeting shall be held on the first Wednesday in October, and another, on the first Wednesday in February.

15 Special meetings may be called by the President by vote of the Council, or by the written request of ten councilors.

Section 2 The deliberations of the Council shall be governed by parliamentary usage as contained in *Roberts Rules of Order*, when not in conflict with the by laws of the Society.

5 Fifty councilors shall constitute a quorum.

Section 3 The Council at its annual meeting on nomination by the Committee on Nominations or from the floor, shall elect by ballot officers of the Society as follows: president elect, who shall serve as president elect until the second annual meeting of the Society after his election and shall unless otherwise voted by the Council become president on his installation in the course of that meeting serving thereafter as president until the installation of his successor, a vice president, secretary, treasurer, and assistant treasurer, all of whom shall assume the duties of office at the close of the annual meeting of the Society and shall hold office until their successors have been duly elected. Councilors only shall be eligible to the offices above named.

20 The Council in event of the death or the incapacity of the President Elect, shall elect a president by ballot, at its next annual meeting on nomination by the Committee on Nominations or from the floor.

25 The Council, at its annual meeting, on nomination by the Committee on Nominations or from the floor, shall elect by ballot a fellow to deliver an oration at the annual meeting of the Society the following year.

30 The Council at its annual meeting shall elect on nomination by the President Elect or from the floor, standing committees to serve for one year from the close of the annual meeting as follows: on Arrangements, on Publications, on Membership on Ethics and Discipline, on Medical Education on Public Health, on Medical Defense on Society Headquarters, on Finance, and on Hospital Relations.

Section 4 The Council shall elect at the stated meeting in October, on nomination by the President or from the floor, the Auditing Committee, composed of two fellows who are not councilors.

5 This committee, following the close of the fiscal year, shall require by a certified public accountant an examination of the assets and securities of the Society in the custody of the Treasurer, and of the Treasurer's books and accounts.

10 This committee shall verify the accountant's examination and report its findings at the stated meeting of the Council in February.

Section 5 The Council may at any meeting fill vacancies in office or elect committee.

Section 6 The Council may vote to establish or abolish sections for the consideration of scientific

papers at the annual meetings of the Society, and shall appoint the first chairman and secretary of a new section so established.

5 Each section shall elect annually a chairman and a secretary to serve for one year from the close of the annual meeting at which they are elected.

10 The duties of these officers shall be to arrange the programs of the meetings of their sections under the rules of the Council.

15 The chairman shall preside at the meetings of the section at the following annual meeting; the secretary shall take charge of the papers presented and shall transmit them promptly to the editor of the official journal of the Society.

Section 7 The Council shall on nomination by the President or from the floor, elect delegates to the House of Delegates of the American Medical Association in accordance with the by laws of that association.

It may, on nomination by the President or from the floor, elect delegates to such other medical meetings as it deems suitable.

Section 8 The Council shall vote the salaries of its officers and employees; the appropriations for its officers and committees, and such other appropriations as it deems suitable.

5 No officer or committee shall exceed the voted appropriation.

No salary to any officer or employee and no regular appropriation shall be increased except on recommendation of the Committee on Finance and by vote of the Council.

10 The Treasurer is authorized, on recommendation of the Committee on Finance, to pay such monies as may be necessary in the event of emergency the existence of which shall be determined by the President.

## CHAPTER V

### CENSORS AND SUPERVISING CENSORS

Section 1 The supervising censors shall constitute a Board which shall meet annually on the day appointed for the annual meeting of the Council. This board shall elect a chairman and also three of their members to sit with the Committee on Membership. Five supervising censors shall constitute a quorum.

10 The secretary of the Society shall act as secretary of the Board. He shall call special meetings at the request of the chairman or five supervising censors. He shall keep a permanent record of the proceedings of the Board and shall provide materials necessary for conducting examinations of applicants for fellowship.

15 The Board at its annual meeting shall adopt a uniform plan for the examination of applicants.

The supervising censors, on request, shall paid traveling expenses.

20 The supervising censors shall be chairmen of their respective boards of censors, and shall cause the examinations of applicants to be conducted in strict conformity to the plan adopted by the Board of Supervising Censors.

25 The censors of the several district societies shall meet for the examination of applicants semiannually on the first Thursday in May and on the first Thursday in December.



The approval of at least three censors shall be necessary to qualify an applicant.

30 An applicant failing two examinations may not again apply until three years have elapsed from the date of the last application.

Section 2. (a) The secretary of a district society may receive, *not later than* February 15 for the censors' examination in May or *later than* September 15 for the examination in December, an application for fellowship submitted on the proper form by an applicant whose legal residence is within the district of that society.

5 The secretary of the Suffolk District Society may receive, and officials of that society may act on, an application for nonresident fellowship.

The secretary of the district society shall verify each applicant's diploma and deliver his application to the Secretary *not later than* February 20 or September 20, respectively.

15 The official journal shall publish, in the first number on or after March 5 or October 5, a list of all applicants. This list shall include name, address, medical school and date of graduation of the applicant; name and address of the secretary of the district society concerned; and if a sponsor is required, the name and address of the sponsor.

20 Fellows are requested to send to the secretary of the district society concerned, *not later than*, respectively, March 20 or October 20, *confidential* written opinions on the qualifications of applicants.

(b) The secretary of a district society shall receive an application from a graduate of a discontinued medical school, a foreign medical school or any medical school not approved by the Council only when:

30 The applicant has possessed a license to practice medicine in the United States or its territories for at least five years;

35 The applicant has submitted with his application the name and address of a sponsor who is a fellow of the district society concerned; and

The sponsor has caused to be delivered by fellows of the Society to the secretary of the district society *confidential* written opinions on the qualifications of the applicant.

40 (c) The censors may admit to examination an applicant who is a graduate of a discontinued, foreign or unapproved medical school only when such applicant has been considered by the board of membership concerned and approved by the Committee on Membership.

The board of membership of a district society shall consist of the president, secretary and supervising censor.

50 It shall gather such information as it deems advisable to determine whether an applicant is conscientious, capable and reputable. It shall interview personally such applicant. It shall either approve or disapprove him for examination by the censors.

55 The secretary of the district society shall deliver to the chairman of the Committee on Membership, *not later than*, respectively, April 1 or November 1, all pertinent correspondence and other data together with the record of such applicant's approval or disapproval, with reasons therefor, by the board of membership.

The Committee on Membership shall have custody of such documents so long as needed and then shall

65 deliver them to the custody of the Secretary; they shall remain *confidential*.

The Committee on Membership shall consider the application of each applicant approved for censors' examination by a board of membership. It shall determine finally whether or not such applicant may take that examination.

70 The Committee on Membership shall not consider the application of any applicant disapproved by a board of membership except on the written request of a majority of that board of membership.

75 Decisions on applications by the Committee on Membership shall be final, and shall remain in force for two years.

80 The Committee on Membership shall notify the secretary of the district society concerned and each applicant considered of its decision *not later than*, respectively, April 20 or November 20.

Section 3. The secretary of each district society shall be the secretary of the district board of censors.

He shall furnish applicants with forms adopted by the Board of Supervising Censors.

5 He shall keep a record of all applicants for fellowship, and see that each applicant pays the examination fee of three dollars, that this fee is sent *promptly* to the Treasurer, that each successful applicant subscribes to the by-laws and code of ethics and within two weeks pays the assessments for the current year.

He shall furnish each new fellow with a copy of the *Digest, By-laws, Code of Ethics, and Medical Defense Act* of the Society.

15 He shall present, on the proper form and promptly after each examination, a bill to the Treasurer for censors' services, together with a list of all applicants examined.

20 The secretary of each district society shall fill out, sign and deliver promptly to the Secretary certificates stating that the successful applicants have complied with the requirements of the by-laws.

Section 4. The censors and secretaries shall be paid from the funds of the Society three dollars for each applicant examined. The amount paid shall be divided equally among those officers attending and taking part in the examinations.

## CHAPTER VI

### OFFICERS

Section 1. The President shall preside at the meetings of the Society, of the Council, of the Executive Committee and of the Committee on Public Relations.

5 He may call a meeting of any committee of the Society.

He shall approve all valid bills against the Society after they have been suitably endorsed by the officer, delegate, or chairman or majority of the committee that has incurred the indebtedness specified in the bill, as provided in Chapter VII, Section 1.

He shall sign the certificates of all delegates, and the diplomas of all new fellows if he is satisfied that they have met the requirements of Chapter I.

15 He shall nominate to the Council all members of committees, all delegates to other medical societies, all fellows to fill vacancies among the officers, councilors, censors and commissioners of trial of the Society, unless otherwise provided by the by-laws or by order of the Council.

He shall make appointments to fill vacancies *ad interim* in any of the offices of the Society

He shall be a member *ex officio* of all committees

He shall, in accordance with specific recommendations by the Committee on Ethics and Discipline, either admonish fellows or appoint a board of trial, as provided in Chapter VIII, Section 1

He shall report on the state of the Society at the annual meeting

He shall call one meeting of the Executive Committee between meetings of the Council, and others at his pleasure

In the event of the death or incapacity of the President-Elect, the President, at the annual meeting of the Council, shall nominate members of standing and special committees, unless otherwise provided in the by laws

**Section 2** In the absence of the President, the Vice President shall perform the duties of the President, and in the absence of both, the senior *ex officio* Vice President in point of membership in attendance shall perform the duties of the President.

**Section 3** The President-Elect shall assist the President in the performance of his duties in such manner as the President may direct and in so doing shall be considered to represent the President

At the annual meeting of the Council following the annual meeting at which he was elected, he shall nominate members of standing and special committees, unless otherwise provided for in the by laws

He shall be a member *ex officio* of all committees

**Section 4** The Secretary shall attend all meetings of the Society, the Council and the Executive Committee, and shall record their respective proceedings in separate volumes

He shall cause to be engrossed and shall sign the diplomas of new fellows if satisfied that they have met the requirements of Chapter I, and shall issue all diplomas and certificates of fellowship

He shall notify fellows of votes by the Council or Executive Committee granting permission to retire, to resign, to transfer district membership or to have dues remitted, and of votes depriving them of or reinstating them in the privileges of fellowship

He shall be *ex officio* secretary of all boards of trial, the Board of Supervising Censors, the Committee on Publications and the Committee on Ethics and Discipline, and shall keep the records of each in separate volumes

He shall have custody of the seal of the Society and of all books, papers, manuscripts, prints and paintings belonging to the Society, except such as are in charge of the Treasurer

He shall issue notices of the meetings of the Council He shall issue to every fellow one month before the annual meeting of the Society a program, listing the time and place of that meeting and of the stated meetings of the Council, the boards of censors for that year, and information concerning the payment of assessments and the distribution of publications, if there are any proposed amendments to the by laws he shall provide that each program is accompanied by a copy thereof

He shall transfer fellows from one district to another under the terms of Chapter III, Section 3,

and shall report to the Society at its annual meeting the changes in membership during the year

He shall conduct official correspondence and shall notify officers, delegates and members of committees of their appointments and of their duties

He shall keep a directory of the fellows, and shall publish the same, under the direction of the Committee on Publications, at such intervals as may be determined by the Council He shall furnish this on request to fellows not in arrears

He shall have jurisdiction over the work of the Executive Secretary

He shall perform such other duties as the Society or the Council may require

**Section 5** The Treasurer shall collect and care for all monies due the Society and shall have custody of the treasury records All monies received by any committee, officer or employee on behalf of the Society shall be paid forthwith to the Treasurer

He shall be bonded in such sum and manner as may be directed by the Council, on recommendation of the Committee on Finance

He shall, under the direction of the Council sue for claims due the Society and shall sell, rent or lease any estate belonging to the Society

He shall pay only such bills as have been countersigned by the proper officer or delegate or the chairman or majority of the committee incurring the indebtedness, as provided in Chapter VII, Section 1, and have been approved by the President

He shall render to the Council at its February meeting a full written report of the assets and liabilities on December 31 of the previous year, and also of the financial transactions of the Society during that year

He shall attend the meetings of the Committee on Finance, furnish the committee with such data as it may require and shall make all investments and reinvestments of the Society's funds with authority to buy or sell securities subject to the approval of this committee

He shall arrange for the Cotting luncheons

He shall familiarize the Assistant Treasurer with the fiscal concerns of the Society

He shall perform such other duties as the Society or the Council may require

**Section 6** The Assistant Treasurer shall assist the Treasurer in the performance of such duties as the Treasurer may direct

In event of the death or the incapacity of the Treasurer, the Assistant Treasurer shall assume the duties of the Treasurer until cessation of the incapacity or the next annual meeting of the Council

He shall be bonded in such sum and manner as may be directed by the Council, on recommendation of the Committee on Finance

**Section 7** The Executive Secretary, under the jurisdiction of the Secretary, shall assist the officers, the Council and such committees as may request his services

He shall hold office at the pleasure of the Executive Committee

**Section 8** The traveling and incidental expenses of the officers and committees elected by districts and of standing committees of the Society, on request shall be paid by the Treasurer, on presentation of an itemized bill duly approved by the President

## CHAPTER VII

## COMMITTEES

*Section 1.* Reports of committees containing recommendations that may require prolonged consideration shall be sent in abstract to the Secretary, at least six weeks before their presentation to the Council, for consideration by the Executive Committee and for publication in the official journal.

Every committee, annually on or before December 10, shall forward, to the chairman of the Committee on Finance, an estimate of its expenses for the ensuing fiscal year, which shall show the purpose of any proposed expenditure of \$100 or more and a similar detailed statement of its expenditures for the current fiscal year to and including November 30 with an estimate of expenditures for the current month of December.

All bills \$100 or more incurred by a committee shall be countersigned by a majority of said committee and forwarded to the President for his approval.

All bills less than \$100 incurred by a committee shall be countersigned by the chairman of said committee and forwarded to the President for his approval.

Every committee shall render a written report to the Council at least once a year.

## COMMITTEES ELECTED BY THE DISTRICTS

*Section 2.* The Executive Committee of the Council shall consist of the President, President-Elect, Vice-President, Secretary and Treasurer and a councilor from each district society, chosen as provided in Chapter III, Section 5.

The Executive Committee shall meet at the call of the President. It shall assist the President in preparing matters for consideration by the Council.

It shall act on all questions of retirement, resignation, remission of dues, deprivation of fellowship for arrears, reinstatement following deprivation of fellowship for arrears, and transfer of fellows from one district to another without change of legal residence.

The Executive Committee may appoint and dismiss the Executive Secretary.

It shall authorize or confirm action by the officers in emergency.

The Executive Committee shall perform such other duties as the Council may require.

*Section 3.* The Committee on Public Relations shall consist of the President as chairman and one councilor from each district society, elected as provided in Chapter III, Section 5.

It shall concern itself with the relations between fellows of the Society and the public.

*Section 4.* The Committee on Legislation shall consist of one fellow from each district society, elected as provided in Chapter III, Section 5.

It shall study, initiate and support measures to improve standards of medicine and promote the public welfare. It shall study and oppose such measures as it may deem contrary to the public welfare.

It may employ counsel, subject to approval of the President.

District legislative committees shall be auxiliary to and under the direction of this committee.

*Section 5.* The Committee on Nominations shall consist of one councilor, with another as alternate, from each district society, as provided in Chapter III, Section 5.

It shall nominate the officers and orator of the Society, and shall cause its report to be published in the notice of the annual meeting of the Council.

## STANDING COMMITTEES

*Section 6.* The Committee on Arrangements shall consist of five fellows.

It shall be responsible for all arrangements for the annual meeting of the Society.

The chairman shall furnish the Secretary, on or before April 15, with all the data necessary for the annual program.

The secretary of this committee shall record its proceedings in a volume which shall be filed with the Secretary.

*Section 7.* The Committee on Publications shall consist of five fellows.

It shall supervise the publications of the Society.

It shall publish, when ordered by the Council, a directory of the officers and fellows.

It shall appoint the Shattuck Lecturer in accordance with the provisions of the Shattuck bequest.

It shall inform all readers of papers and discussers of the following rules:

All papers presented at the meetings of the Society shall be the property of the Society. No paper presented in the section meetings at the annual meeting shall occupy more than thirty minutes in its delivery. Each discussion shall be limited to five minutes, unless lengthened by vote of the meeting.

All papers shall be ready for publication, typewritten and accompanied by suitable material for illustrations, if any, when read to the sections or to the Society; and as soon as read they shall be handed to the secretary of the section or of the Society for transmission to the editor of the official journal.

Discussers shall correct and promptly return to the editor for publication, if deemed proper by this committee, the stenographer's transcribed notes of their remarks.

*Section 8.* The Committee on Membership shall consist of five fellows.

It shall consider applicants applying for fellowship according to the provisions of Chapter V, Section 2c.

It shall consider matters relating to honorary or associate fellowship, retirement, resignation, remission of dues, deprivation of fellowship for any cause, reinstatement following deprivation of fellowship for arrears, transfer of fellows from one district society to another, as provided for in Chapter III, Section 3, and shall make recommendations to the Council or the Executive Committee, as provided in Chapter I, Sections 10 and 11.

This committee shall confer with the representatives of the supervising censors as provided in Chapter V, Section 1.

*Section 9.* The Committee on Ethics and Discipline shall consist of five fellows.

It shall investigate and consider, either on charges submitted in writing or on its own initiative, any alleged or apparent offense on the part of any fellow, as provided in Chapter I, Section 9.

It shall either admonish him, request his resignation or report its findings to the President with its recommendations, if as a result of its investigations and after a hearing that has been requested by the fellow, the committee finds that he is guilty of such offense

The President acting on such recommendations shall (a) censure the fellow, or (b) refer the matter to a board of trial, as provided in Chapter VIII, Section 1

A member of the committee shall act as prosecuting officer in cases that come before a board of trial

**Section 10** The Committee on Medical Education shall consist of five fellows

It shall consider matters relating to medical education

It shall annually revise, subject to approval by the Council, the list of recognized medical schools and colleges

**Section 11** The Committee on Public Health shall consist of five fellows

It shall foster the knowledge of the prevention and treatment of disease by any appropriate measures

**Section 12** The Committee on Medical Defense shall consist of five fellows

It may appoint as auxiliary members one fellow in each district

It shall act, under the provisions of the Medical Defense Act, on applications of resident fellows for legal services in the defense of suits for alleged malpractice.

It may take counsel with both plaintiff and defendant in threatened suits

It shall report to the Committee on Ethics and Discipline any instance coming to its knowledge wherein a fellow, in connection with a suit for malpractice, has violated the code of ethics of the Society

**Section 13** The Committee on Society Headquarters shall consist of five fellows

It shall supervise the maintenance of the Society Headquarters

It shall acquire funds for expansion, subject to approval by the Council

**Section 14** The Committee on Finance shall consist of five fellows

It shall recommend to the Council, at the February meeting, the budget for the current fiscal year

The budget shall show in detail the proposed expenditures and their allocation to the various officers, employees, committees, or any other person or persons authorized to expend the same, and shall make available to any fellow on request the purpose of any proposed expenditure of \$100 or more. The budget shall include for purposes of comparison similar items of expenditure for the previous year, if any

It shall consider requests for extraordinary appropriations and shall refer them, with recommendations, to the Council for action

It shall, at the close of the fiscal year after consultation with the Treasurer and with the approval of the Council, determine the amount to be refunded to the several district societies from the unexpended balance on December 31. This amount

shall be apportioned among the district societies according to the number of annual assessments paid to the Treasurer before March 1

**Section 15** The Committee on Hospital Relations shall consist of five fellows

It may appoint as auxiliary members one fellow in each district

It shall concern itself with the relations between the fellows of the Society and hospitals

## CHAPTER VIII

### BOARDS OF TRIAL

**Section 1** A board of trial shall consist of five of the commissioners of trial, appointed by the President, to consider charges against a fellow recommended for trial by the Committee on Ethics and Discipline.

The President shall designate a time and place for the meeting of such board and shall cause due notice thereof to be given to the complainants and to the accused, and to all members of the district society of which the accused is a member

A board of trial may hear fellows who appear in the interest of the accused, but legal counsel shall be excluded

Failure of the accused to appear or be represented at the trial shall be considered *prima facie* evidence of the truth of the charges, and a verdict may be rendered accordingly. In case of conviction, a board shall recommend such sentence as it shall deem best, as provided in Chapter I, Section 10. The Secretary shall enter on the records the proceedings of each board of trial and shall report them to the Society at the next annual meeting for final action

The Secretary shall notify the accused of the findings of a board of trial and of the action of the Society thereon, and he shall notify the several district societies of the sentence imposed

**Section 2** Each commissioner, and each prosecuting officer, shall be paid ten dollars a day for attendance plus his incidental expenses

It shall be a duty of any fellow summoned by the Committee on Ethics and Discipline to appear as a witness before a board of trial. No fellow shall be relieved of this duty without an excuse satisfactory to such a board

## CHAPTER IX

### AMENDMENTS

These by laws may be amended by a majority vote at any annual meeting of the Society, provided the proposed amendment or amendments shall have been submitted previously in writing to the Council, shall have been approved by that body by vote, and shall have been published and forwarded to each fellow, along with the program of the meeting of the Society wherein they are to be considered.

## DEATH

BONNEY — ROBERT BONNEY, M.D., of East Boston, died March 22. He was in his eighty fourth year

A native of Philadelphia, Dr Bonney received his degree from Harvard Medical School in 1898. He was a fellow of the Massachusetts Medical Society and the American Medical Association

He is survived by a brother

## WAR ACTIVITIES

### CIVILIAN DEFENSE

#### FIRST AID FOR AIR-RAID CASUALTIES

First-aid measures applicable to the emergencies of war are embodied in a booklet, *Handbook of First Aid*, issued by the Medical Division of the Office of Civilian Defense in co-operation with the American National Red Cross, for the use of enrolled civilian-defense workers.

The handbook is of pocket size and has twelve chapters titled as follows: "Advice to the Civilian Defense First Aid Workers"; "General Considerations"; "Care of Wounds"; "Dressings and Bandages"; "Hemorrhage"; "Burns"; "Shock (Collapse)"; "Fractures"; "Artificial Respiration"; "Transportation of the Injured"; "Chemical Warfare"; "Miscellaneous Conditions." As indicated by the titles, all material not relevant to the war emergency has been omitted from consideration. The book does not replace the standard Red Cross *Textbook of First Aid*, which is to be used in first-aid classes.

First-aid measures are described within the framework of the plan for emergency medical service: that is, they are described as they will be carried out under war conditions. Numerous illustrations clarify such procedures as the tying of bandages, pressure to stop hemorrhage, the application of traction splints and methods of transporting the injured. Throughout the handbook, the first-aid worker is cautioned against any action that should be left to a physician or any that would handicap the physician when he arrives. One of the cardinal principles emphasized is, Remember you are a first-aid worker and not a physician. For example, the worker is taught not to apply any antiseptic to a wound and not to apply an ointment or a salve to a burn.

About twenty pages are devoted to a discussion of fractures, with detailed descriptions of fixed traction splints for the upper and lower extremities, as well as improvised splints.

The chapter on chemical warfare describes types of war gases and lists briefly under each type the characteristic effects it produces and the appropriate first-aid measures. This chapter also includes instruction on care of burns caused by incendiary bombs containing phosphorus.

The last chapter covers heat stroke, heat exhaustion, heat cramps, frostbite and carbon monoxide poisoning. In connection with the injuries from heat and cold, it is pointed out that an enemy attack can occur at any season and that both victims and defense workers may be exposed to extremes of temperature for many hours.

## CORRESPONDENCE

### POLITICS: A PARALLEL TO MEDICINE

*To the Editor:* When we say that a man is a "good politician" we know what the term implies: that he is intellectually dishonest; that he is more or less a demagogue who plays on the passions of the people; and that he is untrustworthy, promising benefits that he knows are impossible to grant.

We have come to accept this standard set by the politicians as a necessary evil, as something unchangeable and permanent. We do not tolerate it in any other human relation or any other walk of life. Even the business and financial worlds, which are supposed to have low ethical standards, have a code of morals. A Wall Street broker is ostracized if he breaks his promise or his word in a financial transaction. A research worker in medicine who,

to gain a temporary notoriety, intentionally publishes claims known by him to be false is forever outlawed by the profession.

For half a century, we have turned the country over to third-rate and fourth-rate politicians to govern. With a few exceptions, they have chosen politics as a career for reasons other than service to humanity. It is only necessary for a Lincoln to arise to be aware of the gulf between a man of integrity and vision—a man who not only would not lie but could not lie—and the army of men in the municipal, state and federal governments whose regard for telling the truth is mostly theoretical and whose conception of a promise is that it is a temporary expedient and can always be broken after a reasonable length of time. It is strange that politicians do not realize that there is no quality in a man either in public or private life that commands more intense respect and admiration than intellectual honesty. After many years in political life, a politician has compromised his principles so many times that he has ceased to have any principles. Ideals that he once may have had he is apt to view with derision and contempt. He becomes calloused and hard, and speaks the language of the street and gutter.

In the recent mayoralty election in New York City, a prominent politician, in a fifteen-minute radio address, called Mr. LaGuardia a demagogue, a mountebank, a hypocrite, a guttersnipe and a "mucker run amuck." Such freedom of expression seems to be peculiar not only to the vulgar and the low but to politicians as well.

To such men as these,—opportunists, demagogues, grafters and men whose word cannot be trusted,—humanity has entrusted its life, its freedom and its property. By their fruits they are known. The universal woe is a measure of their leadership.

And now a river of blood encircles the earth. And now our young men clean and strong and unbesmirched go forth to die in foreign lands by hideous ways to serve the ends of men called great. These, our sons, so innocent, so gay, shall water the earth with their blood. Guiltless, they are chosen to pay for our folly and greed. They shall lie stabbed and torn and shriveled with fire. Junes will come and go. They will not feel the hot sun or the south wind's warm caress. They will not see the meadows spotted with yellow and gold or the bobolink swaying on slender reed, or breathe the scent of pine and the new cut hay. They are the dead; and all the promise of their youth is blasted in the bud.

So this ignoble breed has set the style for politics in this country. We accept it as a matter of course. It never occurs to us that the style could be changed like women's hats. We have no vision and no conception of the change that would occur if a few thousand high-minded, cultured young people entered political life. If one has ever planted grass seed, one knows that if enough seed is planted only a few weeds will grow. If it is, cultivated carefully, weeds will cease growing entirely.

Until recently, the educated and well-to-do classes of society in this country have had nothing to do with politics. It is a dirty business, and the better elements do not want to soil their hands with it.

A while ago, I read a history of medicine, and I noted a parallel between medicine as practiced one or two hundred years ago and politics, domestic and world politics, as practiced today. If we look on war as a plague and poverty and inequality of opportunity as a disease, we shall appreciate the similarity of the problem and the similarity of the attitude of the public toward it.

A hundred and fifty years ago, the average span of life was twenty years. It is now sixty. The principles of mod-

in medicine were unknown. There was no sanitation. Pestilence and disease were present all the time. Every 10 years or so, Europe was swept with one plague or another: bubonic plague, smallpox, typhus, typhoid fever, and cholera came in their turn. Tuberculosis, diphtheria, and scarlet fever in virulent form were endemic all the time. It is stated that one epidemic of bubonic plague in the Middle Ages removed a third of the population of Europe. In this country, at the beginning of the nineteenth century, an epidemic of yellow fever killed fifty thousand people in Philadelphia.

These plagues were thought to be due to acts of God. To punish the people for their sins. Cotton Mather was a strong exponent of this idea. Religion dominated medicine, and it was considered a blasphemy if anyone questioned the act of God, and made an effort to discover the cause of disease. To dissect a human body for the purpose of learning its anatomy was considered a desecration of the temple of God and was prohibited by law. So there was no chance of learning even the fundamentals of medical science.

People accepted plague, just as we today accept wars, as something inevitable. We hear that man is a fighting animal, and if the impulse to fight is curbed he will degenerate. The Nazis have said that war is a desirable thing and hence they make a virtue of it.

In those days, doctors were, for the most part, ignorant men. The surgeon was a barber, and the physicians came from equally humble walks of life. Moliere, in his plays, gives expression to the contempt of the public for the medical profession. The doctor was a constant butt for ridicule. *The ridicule was justified for he was more or less a humbug, just as the politician is today.* He tried to cover up his ignorance by pomposity and putting on a front. He cultivated a bedside manner, used long words and wrote his prescriptions in Latin. To impress his patients he wore a high hat and frock coat and carried a gold-headed cane. He talked a jargon that would be entirely unintelligible to physicians today. His theories concerning the causes of disease and its treatment were almost entirely wrong. Very little of value has come down to us. For almost every ailment, he prescribed bleeding. A sick person in those days was indeed fortunate if he escaped the clutches of a physician.

A century ago, the causes of diseases were unknown. Every doctor had his private theory. It was usually in conflict with that of his confreres and gave rise to bitter controversies and ill feeling in the profession. Today we see the parallel of this among economists, politicians and planners of one kind or another. There are as many theories of economy today as there were theories of disease in the dark ages of medicine.

Up to a century ago then, man was still living in the Middle Ages, so far as knowledge of the laws that govern disease and health is concerned. He knew no more about the causes of disease than had been known two thousand years before.

Then a miracle occurred. In France, out of the darkness a light shone out. Louis Pasteur had begun his work. For fifty years he carried on his researches to determine the causes of disease in human beings and animals, the blight of the silkworm and the fermentation of wine. He opened up new worlds for science to explore and became the founder of modern medicine. At the beginning he roused tremendous opposition in the medical profession. His every contention was disputed. He was labeled a charlatan and a humbug. Surmounting the greatest abuse ever directed against any scientist, his ideas at last prevailed. A little group in England headed by

Lister adopted his principles. Semmelweis in Austria put them into practice. Oliver Wendell Holmes in the United States listened and introduced his ideas to Boston.

One by one, the plagues that had decimated mankind for hundreds of years were brought under control. Out of the confusion and ignorance that medicine was a hundred years ago,—when superstition quickened and the blind following of tradition were the chief characteristics of the profession,—has grown a mighty system of healing that has spread to all the corners of the earth. Medical science has no secrets, no discovery is patented. It has dedicated itself to the service of mankind. It advances by leaps and bounds. Every week there is a new discovery. It may not be too rash to prophesy that the dream of the ages will be realized that sickness and disease will be banished from the earth. Pasteur's precept still holds in laboratories, hospitals and medical schools the world over. It is very simple—on the hearts and minds of every research worker and medical student is written the command: Seek the truth, follow the truth, tell the truth.

Might not the politicians, might not we all, learn something from the study of the history of medicine? In it, a century ago, one of the greatest revolutions in all history occurred. It was not like an ordinary upheaval conditions reverting to their former state after a period of time. It was a permanent and beneficent revolution, which started an evolutionary process that with ever widening circles has continued to this day. It set new standards, it created a new atmosphere in which reason, truth and knowledge flourished and flowered. It was democratic, it was international—*medical men the world over speak the same language. It sought not to enrich itself, it was governed by no commercial motives, it built no monopoly, it sought only to create a better and healthier world for men and women to live in.*

It is said that wars are inevitable and impossible to eradicate. Must not a mother have said two hundred years ago, sitting by the bed of her dying child, 'It is an act of God, we must suffer for our sins'?

Following the work of Pasteur, thousands of young men of the highest type in all parts of the world began crowding into medical schools and laboratories as volunteers in the new crusade. Today, are our imaginations so feeble that we are unable to visualize the results of thousands and tens of thousands of honorable and intelligent young men and women entering political life, crushing by weight of numbers the forces of greed, dishonesty and hate that now rule the world? If grass seed is sown thickly enough, the weeds will not grow. When that happens, it will be the greatest of all crusades.

NEIL C STEVENS, M.D.

Walpole, New Hampshire

## REPORT OF MEETING

### JEWISH MEMORIAL HOSPITAL

At a regular meeting of the Jewish Memorial Hospital in Roxbury on December 3, Dr. Joseph H. Pratt, of the Pratt Diagnostic Hospital, discussed Recent Phases of Pancreatic Disease. He stated that the incidence of carcinoma of the pancreas is not nearly so rare as its clinical recognition indicates. It has been reported that 0.5 to 10 per cent of all autopsies reveal this condition. Engleman in San Francisco, however, reported an incidence of 2.1 per cent of all post mortem examinations and 9 per cent of all cancers found in the series. Its anatomic position

and relations make this organ difficult to palpate even in cases of cancer, but often result in signs and symptoms referable to the biliary tract or duodenum.

From a physiologic standpoint, Dr. Pratt said that the pancreas is an important factor in the digestive functions of the body. Its trypsinogen is converted by the enterokinase of the intestinal tract into the active enzyme, trypsin, which aids in the digestion of protein. In addition, there are diastase for the digestion of starches and lipase for that of fats. Furthermore, a useful alkaline medium, whose presence, incidentally, is often a more significant diagnostic point than that of the ferments, is supplied. The amount of fluid secreted may equal as much as 1500 to 2000 cc. per day, whereas the injection of secretin may call forth as much as 100 to 500 cc. in a single hour. The external pancreatic juices were formerly not considered essential for the maintenance of health and life, and are still ignored in most operations for carcinoma of the pancreas; this belief is now known to be a fallacy. Ligation of the pancreatic ducts results in an elevated blood diastase for several months, and huge doses of pancreatin (5 to 10 gm. daily) are necessary to offset this lack.

The elevation of the blood or urinary diastase has become a valuable test in the diagnosis of acute pancreatitis. This was first noted in 1922, when acute edema without necrosis was originally recognized, but is also present in acute hemorrhagic pancreatitis with fat necrosis. Failures in the use of this test can be attributed to the late application of the test or the late examination of the urine. Even if the disease is progressive, the diastase values return to normal after forty-eight hours at the latest, but they are invariably positive during the first twenty-four hours. The urine is more frequently positive than the blood, but must be examined within two hours of voiding. The importance of making the diagnosis is reflected in the statistics, which reveal a decrease in mortality from 60 or 70 to 25 per cent or less by refraining from operation in acute pancreatitis. The diastase values have been found significantly elevated in no other condition. The test should be carried out daily so that a curve rather than a single determination may be available for the following of a suspected case.

The stools serve as an excellent guide in cases of pancreatic disease and in differentiating jaundice from other causes. In any obstruction of the pancreatic juices, the stools are bulky, light colored and foul smelling. The lack of color persists even in the presence of sufficient bile from the biliary tract. Microscopically, there are fat globules and crystals, as well as muscle fibers, if meat has been ingested. This latter observation is essential in the differential diagnosis of tropical sprue, which is a disturbance in fat digestion only.

In acute edema of the pancreas, the epigastric pain is usually severe, but not agonizing, and can be controlled with morphine in contradistinction to acute hemorrhagic necrosis. The pain may easily be confused with that of acute gall-bladder colic and may be differentiated only by the diastase test. Again, the value of daily determinations is brought out, for if the values return to normal on the second or third day the diagnosis becomes clearer. Such attacks, however, are usually associated with cholecystitis, and the subsequent removal of an affected gall bladder should be carried out, to guard against recurrences and possible acute hemorrhage.

Dr. Pratt described the double-barreled gastroduodenal tube, which has proved so helpful in the study of the pancreatic secretions. It has openings in the stomach portion to allow for decompression of that organ, then

a closed part, then openings in the duodenum that are drained through a separate tube and thus allow separate analysis of stomach and duodenal contents. In the normal person, the intravenous injection of secretin causes a rapid increase of the duodenal contents and a decrease in the amount of bile. Pure pancreatic juice is obtained only in the presence of a normal gall bladder. Normally, there is also a rapid rise in the duodenal alkalinity on the injection of secretin. This test has been employed in an attempt to diagnose carcinoma of the pancreas, in which all the functions of the gland are diminished. In 3 cases in which the stools did not indicate this disease, the secretin test revealed a low volume and a low alkalinity. Acute pancreatitis seems to run normal values in the limited number of cases observed. In cancer, the values for trypsin, lipase and diastase in the duodenal drainage are also low.

In discussing the diagnosis of carcinoma of the pancreas, Dr. Pratt pointed out that painless jaundice is greatly overstressed. Pain is actually a prominent symptom in approximately 60 per cent of cases, and may occur without jaundice. The diagnosis is seldom made without jaundice. In Engleman's series, loss of weight occurred in virtually 100 per cent of the cases, and this has been corroborated at the Pratt Diagnostic Hospital. The amount varies from 10 to 40 pounds. The second most constant finding in both series was that of abdominal pain. This is not characteristic in type, may occur anywhere in the abdomen, and is not necessarily constant. Jaundice is also found in about 60 per cent of cases but is present as a late sign, as shown by the fact that it was of less than six weeks' duration prior to death in over 65 per cent of Engleman's cases. Blood in the stools was found in 75 per cent of those at the Pratt Diagnostic Hospital but in only 13 per cent by Engleman. Dr. Pratt has also observed an elevated blood-sedimentation rate in 75 per cent of his cases, and diabetes in 25 per cent. Also noted was a tendency for the patient to be unduly nervous.

In answer to questions, Dr. Pratt stated that he believes that the sphincter of Oddi is really a sphincter and that the finding of pancreatic ferments in the gall bladder indicates an elevation of pressure. Probably a common channel is the explanation of the association of acute edema of the pancreas with biliary disease. He considers "acute hemorrhagic pancreatitis" a misnomer, the condition being one of intoxication rather than of infection. If such a patient is operated on inadvertently and the condition is recognized,—which should always be easy,—the abdomen should be closed immediately, without exploration or drainage.

## BOOK REVIEW

*The Microbe's Challenge.* By Frederick Eberson; Ph.D. M.D. 4°, cloth, 354 pp., with 1 portrait. Lancaster, Pennsylvania: The Jaques Cattell Press, 1941. \$3.50.

Of all the popular books on bacteriology written in recent years, the reviewer considers this publication outstanding. Soundly and accurately written, in language only technical enough to make the meaning clear, the work covers the entire field of microbes and their relation to illness in man. A glossary, index and suggested readings complete the volume. There are no illustrations, a fact that does not detract from the value of the book. Here is a publication that will appeal to any intelligent layman and should find a place in every public library as a standard reference text.

(Notices on page x)

# The New England Journal of Medicine

Copyright 1947 by the Massachusetts Medical Society

VOLUME 226

APRIL 9, 1947

NUMBER 15

## REGIONAL ENTERITIS

### Report of Forty Three Cases

RICHARD WARREN, MD \* AND RICHARD H. MILLER, MD †

BOSTON

SINCE 1932, when Crohn, Ginzburg and Oppenheimer<sup>1</sup> awakened widespread interest in regional enteritis, there have been numerous reports of cases in the literature. Few of these have added much to the understanding of the disease. The clinical picture as originally described is still the only aspect of regional enteritis that is well understood. The pathology, diagnosis, prognosis and the most desirable treatment are as yet in completely understood. The etiology is entirely obscure.

From 1930 to 1940, inclusive, 43 cases of regional enteritis were treated at the Massachusetts General Hospital, many of them on the private wards. This article deals chiefly with the results of the treatment of these cases.

#### CLINICAL PICTURE

Crohn and his associates<sup>1</sup> described four stages of regional enteritis: the acute (simulating appendicitis), the diarrheic, the obstructive and the fistulous. In the present series, at the time of admission, 6 cases were acute, 15 were diarrheic, 13 were obstructive, and 4 were fistulous. Five cases were encountered that represented a fifth, or symptomless, stage, most of these were discovered by x-ray at routine gastrointestinal study of symptoms that could not have been caused by regional ileitis. One case, however, was more definite. A pyloroplasty was performed for a proved duodenal ulcer, and at routine exploration of the abdomen a typical regional ileitis was found, both by palpation and by observation. This persisted and was confirmed later by x-ray study, but never caused any symptoms.

The 4 patients who presented themselves with intestinal fistulas had had previous operations. Two additional cases developed fistulas following

operative procedures in this hospital. None of the cases developed fistulas without operation. It is accordingly apparent that the four classic stages of the disease are not necessarily consecutive. The fistulous stage often comes directly after the acute stage, usually following an appendectomy. This fact has been emphasized by Ginzburg.<sup>2</sup>

In the present series, as in those reported by others, regional enteritis was commonest in relatively young people, the average age being thirty, with extremes of fourteen and fifty seven years. Lunich and Crohn<sup>3</sup> have recently reported the oldest case yet recorded, in a patient aged seventy. There is no predilection for race, since only 11 of our cases occurred in Hebrews, and although the ratio of females to males was 29:14, no constant sex predominance has been found in larger series.

In the 33 cases in which data on stools could be obtained, there were only 2 patients whose stools were positive for occult blood or who gave a history of bleeding. This low incidence of intestinal bleeding is in accordance with the experience of others but is surprising in view of the fact that mucosal ulcerations are such a characteristic part of the pathology of the disease.

In our series, the terminal ileum alone was involved in 27 cases, the terminal ileum and the cecum were the site of the lesion in 10 cases, and other areas of small bowel were involved in 6. Ravdin and Johnston,<sup>4</sup> in a survey of the literature, found that the site of the lesion was as follows: terminal ileum alone, 261 cases; terminal ileum and cecum, 100 cases; and other areas of the small bowel, 2 cases. Granulomatous processes in all parts of the gastrointestinal tract have been described. Although several cases of unusual granulomatous inflammatory lesions primary in the stomach or colon have come to our attention, the pathologic findings have not been definite.

\* Assistant in Surgery, Massachusetts General Hospital, and Assistant in Surgery, Harvard Medical School.  
† Fellow for Board of Consultation, Massachusetts General Hospital.



enough to warrant their addition to this series of cases.

Fissure or fistula in ano is a common accompaniment of regional enteritis, and 9 patients had had one or the other at some time in their lives. There is no implication that these lesions are a part of the primary pathologic process. It is rather to be supposed that they are secondary to irritating diarrhea, which so often occurs in ulcerative colitis. No interintestinal or intestinoperineal fistulas were encountered in this series, although such lesions have been described as not uncommon.<sup>1</sup>

### DIAGNOSIS

The diagnosis of regional ileitis is made in one or more of three ways: pathological examination, gross observation at the operating table, and x-ray study. In all the cases in our series, evidence of the disease was demonstrated by at least one of these methods. A diagnosis of regional ileitis was made by x-ray study in 16 of 30 cases that were later proved by operation; no definite x-ray diagnosis was made in 11 cases. In only 3 cases was the disease present when the involved region had appeared normal on x-ray examination. The four x-ray signs of Kantor<sup>8</sup>—the "string" sign, the filling defect in the terminal ileum, the dilated intestine above it, and the conical shape of the barium shadow—were of use in some of the advanced cases, but x-ray study was also helpful in many cases before these signs were evident. The so-called "motility" gastrointestinal series, with the taking of hourly plates to visualize the barium in the terminal ileum, was of the greatest value. We have not used the Miller-Abbott tube, as Boon<sup>9</sup> has done, to make the examination simpler, but this has definite points of merit, the chief of which is the ability to use, thereby, a much smaller amount of barium. We look forward to employing it in the future when the occasion arises. We are of the opinion that, whether or not disease is discovered by the gastrointestinal motility series in the terminal ileum, completeness demands that a barium enema be administered. One patient, who underwent a very radical resection of the right colon and lower ileum, had a prompt subsequent appearance of the disease in the left colon. It was not certain that the disease was absent in this area at the time of the original operation because a barium enema had not been given. A patient with regional ileitis deserves as complete a preoperative study of the intestinal tract as it is possible to give him.

### PATHOLOGY

The typical pathologic picture of regional enteritis is that of a chronic granulomatous process

in the intestinal wall and mesentery. Crohn, Ginzburg and Oppenheimer<sup>1</sup> considered the disease a pathologic entity consisting of chronic inflammation that started in the serosal coat of the intestine and later involved the mucosa in edema, ulcers and pseudopolyps. The mesentery partakes in the edema, so that the mesenteric fat enlarges and apparently creeps up onto the intestinal wall, giving the impression that the intestine has sunk into its mesentery. Many observers, however, have regarded it as a nonspecific process from the pathological viewpoint.<sup>10, 11</sup> The microscopic appearance, which consists in chronic inflammatory elements, fibroplasia, occasional giant cells and even epithelioid cells, could be caused by any bacterial agent or foreign body capable of producing low-grade inflammation, and in this sense, the picture is nonspecific. A considerable degree of uncertainty also envelops certain patients with fistulas in whom secondary infection so destroys the accustomed pathologic appearance that the diagnosis is made rather by the clinical behavior of the disease than by the appearance of the diseased tissue.<sup>2</sup> Hadfield<sup>12</sup> found only 13 of 20 cases of regional enteritis that presented characteristic giant-cell lesions. The histology in the early cases that are discovered at operation for acute appendicitis is also not clear, for few specimens of the intestine are available for study at this stage. In the patients who are seen in this stage and recover spontaneously, it will always be impossible to make an accurate diagnosis. Strongly supporting the belief that the pathologic features of the disease are difficult to define as an entity is the fact that during the last nine years, although hundreds of clinical articles have been written on the subject, pathological journals have been extremely silent concerning the disease. It is probable that further definition of this aspect of regional enteritis will await discovery of the etiologic agent.

### ETIOLOGY

Lengthy discussions of the different theories concerning the etiology of the disease have been published.<sup>4, 7</sup> Although interesting suggestions are made by various authors, no one holds a strong brief for his own theory. Perhaps the most promising hope lies in the search for some agent that primarily obstructs the mesenteric lymphatics. Whether this is a lipoid,<sup>10</sup> some form of silica,<sup>13</sup> or a virus is entirely unknown. The similarity or relation of the disease to lymphogranuloma inguinale, to Johne's disease of cattle,<sup>14, 15</sup> to chronic dysentery,<sup>16</sup> to tuberculosis, to sprue<sup>17</sup> and to Boeck's sarcoidosis is interesting but uninformative.

## TREATMENT

It was at first thought that, since regional enteritis was a specific disease affecting most commonly the terminal ileum, an area so amenable to successful surgical resection, surgery should be

TABLE 1. *Results of Treatment in Cases Reported in the Literature.*

AUTHOR	TYPE OF TREATMENT	TOTAL NO OF CASES	PATIENTS RECOVERED OR IMPROVED	PATIENTS UNIMPROVED	DEATHS IN HOSPITAL
Dixon <sup>18</sup>	Detour operation	14	5	5	4
	Resection	29	24	3	2
Crohn <sup>19</sup>	No operation	11	3	8	
	Operation		36	3	(10-15%)
Mixer <sup>20</sup>	Operation	278		(20%)	(14%)
Kavdin and Johnston <sup>4</sup>	Resection	88	60		
	Detour operation	290	89		
Cutler <sup>14</sup>	Resection	8	2	5	1

the therapeutic method of choice in all cases. It was soon realized, however, that many of the "early" cases either were not regional enteritis or underwent spontaneous regression. Therefore, the form of treatment that has been almost universally advocated has been surgical resection in all

basis for his advocating conservative treatment of all cases; the results from detour operation, or ileocolostomy, are not so good as those from resection; and the operative mortality from resection is about 15 per cent.

Table 2 presents an analysis of the cases at the Massachusetts General Hospital. It reveals the disturbing fact that, although 26 patients had resection\* with only 1 operative death, only 6 of these were symptom free on follow-up inquiry, and only 2 more were not incapacitated by recurrence or persistence of symptoms. Of the 5 patients who had ileocolostomy or detour operations alone, 2 are well, and 3 died later. It is unfair to compare the ileocolostomy group with the resection group because the ileocolostomy often precedes the resection: in other words, if a patient has an ileocolostomy done and continues to have symptoms, but is not too sick for further surgery, a resection is usually performed. The only cases, therefore, that remain for analysis as "ileocolostomies" are those in which the patients got well or those in which they became worse and died. These factors should be taken into account when one considers the poorer results from detour operations as reported in the literature. It has recently been suggested that the reason ileocolostomy

TABLE 2. *Results of Treatment in 43 Cases at the Massachusetts General Hospital*

TYPE OF TREATMENT	TOTAL NO OF CASES	RECOVERY	PERSISTENCE OF SYMPTOMS			DEATHS	
			NO INCA PACI TATION	PARTIAL INCA PACI TATION	TOTAL INCA PACI TATION	IN HOSPITAL	LATER
Resection	26						
First stage	16	2	1	5	6	1	1
Second stage	10	4	1	2	2	0	1
Detour operation	5						
Complete	4	1	0	0	0	0	3
Partial	1	1	0	0	0	0	0
Conservative	12	5	4	1	0	1	1
Totals	43	13	6	8	8	2	6

cases of the disease that were well established, but conservative therapy in the early, acute cases. The results of this policy are not easy to evaluate either in the cases reported in the literature or in those of our series. The length of the follow-up, the criteria for diagnosis, the stage and extent of the disease, and the magnitude of the resection performed are vital data but, unfortunately, are all too scant.

Table 1 gives a summary of the results of treatment in the significant series from the literature. There are four points of interest in this table: Dixon,<sup>18</sup> Crohn<sup>19</sup> and Mixer<sup>20</sup> all report 80 to 90 per cent of good results from resection; Cutler's poor results from resection form a sharp contrast to those of the first three authors, and are the

is unsuccessful in relieving symptoms is that most surgeons do it without transecting the ileum distal to the anastomosis and thus do not ensure complete diversion of the fecal stream from the diseased area. It is certainly logical to suppose that if ileocolostomy alone is to be done, the procedure should be performed in this manner. That this is not a cure-all, however, can be seen from Table 2, which shows that, of the 2 symptom-free patients, 1 had transection performed and 1 did not.

The same difficulty is realized if one compares the patients treated conservatively, in whom the results were excellent, with those treated surgically. The former group comprises, with 1 exception, patients in the acute and less established phase of

\*Two patients had the original resection at other hospitals

the disease. It is obvious that no conclusion can be drawn from conservative versus radical treatment in established regional enteritis unless alternating cases are treated by the two methods. The exception referred to above, however, is instructive. The patient was a thirty-year-old married woman who had suffered from diarrhea and inability to gain weight for six years. Her case was followed for two years. There was definite x-ray evidence of regional inflammation in the terminal 46 cm. of the ileum. This was the one patient in the partially incapacitated group who was conservatively treated. She is able to do all her housework except for occasional periods when she becomes slightly overtired or emotionally upset; the usual diarrhea of two or three stools a day then changes to six or seven a day for a week or so. This occurs approximately every three or four months. A recent x-ray film shows very slight progression of the disease. The patient presents a problem somewhat similar to many who have had unsuccessful reactions.

An attempt was made to analyze the individual cases treated by surgery with a view to finding an indication of why some of the operations were successful and some not. The three important recommendations made by most authors were kept especially in mind: to resect the diseased area, leaving a wide margin of normal intestine between it and the transection; to search for and remove "skip" areas; and to resect widely the involved mesentery and its lymph nodes. Since these 31 patients were operated on by eighteen different surgeons, there was no strict uniformity of operative treatment in this series, and the records of the operative procedures are not informative on the above topics. In 3 of the cases that were unimproved by resection, however, the definite statement is made that the resection was done well beyond the diseased intestine. A specific statement that skip areas were not present was not made, but since in each case the recurrences were in the region of the previous resection, it seems that, even had skip areas been present, they could not have been responsible for the recurrence. It is also confusing that 1 patient, who is now symptom free, presented himself with disease in the ileocecal region and in five skip areas elsewhere in the small intestine. Resection of the ileocecal region and only one of the skip areas was done, leaving four that have caused no trouble.

On the basis of these considerations, it seems that one must agree with Cutler about the low percentage of cures that surgery has to offer. We do not agree with him, however, that, because of this, the medical treatment of the established disease should replace the surgical. It is extremely rare that such patients become spontaneously symp-

tom free as Moschowitz's<sup>21</sup> did. Resection offers a certain percentage—small, perhaps, but nonetheless definite—of cures, and should be advocated when an established case is first recognized as such. By more radical and careful operations and with consideration of the three recommendations of Crohn and Dixon, perhaps our results can be improved. In recurrent cases, it is logical to advocate reoperation only for symptoms that are crippling—namely, uncontrollable infection and obstruction. It is probable that mild or moderate diarrhea alone in these recurrent cases should not be cause for further surgery. Only 1 of 6 cures was the result of a reoperation.

Various specific forms of conservative treatment have been suggested, the chief of which are x-ray therapy and chemotherapy with the sulfonamide group of drugs. One patient, a young boy who died later in tetany, received x-ray treatment without avail when it was first known that his resection had been unsuccessful. We have had no experience with chemotherapy, having been discouraged by the unfavorable report of this form of treatment in one of Rhoads's<sup>22</sup> cases.

#### PROGNOSIS

The prognosis when the disease is not cured by surgery is variable. The patient may fail rapidly, as those with overwhelming secondary infection and fecal fistulas most frequently do (2 patients in our series). There may be remissions, with many years of temporary relief between symptoms (4 cases). The course is most commonly slowly and progressively downward, with gradual weight loss, increase in diarrhea and x-ray evidence of larger areas of intestinal involvement (10 cases). Or the disease may remain, to all intents and purposes, stationary, without evidence of progression (5 cases).

Of the 2 deaths in the hospital, one was from malnutrition in the form of tetany in a young patient who had an acute, severe attack of diarrhea superimposed on a state of chronic, less severe diarrhea of several years' duration. The other patient had tetanic manifestations secondary to failure of calcium and vitamin D absorption; this was associated with failure of absorption of the other fat-soluble vitamins.<sup>23</sup> The deficiencies were controlled in this case by intensive vitamin therapy.

Six patients died following discharge from the hospital after the original operation. As in most diseases, death is the result of a complication rather than of the disease itself. The three complications that are to be feared are extensive infection, malnutrition and intestinal obstruction. Three of the 6 late deaths were from prolonged and extensive infection, which eventually

became uncontrolled. Another case presented vitamin K deficiency as part of the clinical picture. The 2 remaining patients who died after discharge left no clue concerning the cause of death. No patient died from intestinal obstruction per se. The slowly progressive development of obstruction in these cases and the infrequency of gangrene of the intestine result in a type of obstruction that is comparatively simple to deal with.

#### SUMMARY AND CONCLUSIONS

The clinical picture, diagnosis, pathology, etiology, treatment and prognosis of regional enteritis are discussed, and 43 cases are reported.

A fifth, or symptomless, stage of the disease is added to the four accepted stages.

The x-ray examination by the so-called "motility" intestinal series was of great help in diagnosis, being at fault in only 3 of 30 cases.

The pathological picture is not that of a distinct entity.

The various theories concerning the etiology of the disease are mentioned.

The results of surgical resection in established cases in this series were not good, since there were satisfactory results in only 8 out of 26 cases.

Conservative treatment in early cases gave good results.

Since conservative treatment of the established disease, however, gives little hope of cure, radical resection should still be offered these patients as the initial procedure.

The ideal form of treatment of the disease will not be forthcoming until the etiologic agent is discovered.

#### REFERENCES

- 1 Crohn B B, Ginzburg L and Oppenheimer G D. Regional ileitis: a pathological and clinical entity. *J A M A* 4 99 1323 1329 1932
- 2 Ginzburg L. Persistent abdominal fecal fistulas due to regional ileitis. *Surgery* 7 515 528 1940
- 3 Lunich A M and Crohn B B. Atypical regional ileitis: roentgenological limitations. *Am J Digest Dis* 8 185 188 1941
- 4 Rawdin J S and Johnston C G. Regional ileitis: a summary of the literature. *Am J M Sc* 198 769 792 1939
- 5 Kolodny A. Infective granuloma of the stomach: pseudocancer. *Ann Surg* 102 30 33 1935
- 6 Mock H E. Infective granuloma: non specific chronic tumor like productive inflammation of the gastro intestinal tract. *Surg Gynec & Obst* 52 672 689, 1931
- 7 Wilensky, A O. The essential nature of nonspecific granulomatous lesions of the gastrointestinal tract. *Surgery* 6 288 and 452 1939
- 8 Kantor, J L. Regional (terminal) ileitis: its roentgen diagnosis. *J A M A* 103 7016 7011 1934
- 9 Boon T H. Intubation of the small intestine: demonstration and localization of partially obstructive lesions. *Lancet* 1 7 10 1940
- 10 Homans J and Haas G M. Regional ileitis: a clinical not a pathological entity. *New Eng J Med* 209 1315 1324 1933
- 11 Moschowitz E and Wilerky A O. Nonspecific granulomata of the intestine. *Am J M Sc* 166 48 66 1923
- 12 Hadfield G. Primary histological lesion of regional ileitis. *Lancet* 2 773 775 1939
- 13 Reichert F L and Mathes M E. Experimental lymphedema of the intestinal tract and its relation to regional cicatrizing enteritis. *Ann Surg* 104 601 16 1936
- 14 Cutler E C. Cicatrizing enteritis—a neglected clinical entity. *Proceedings Inter State Post Graduate Medical Association of North America*. St. Louis, October 18 22 1937. Pp 137 140
- 15 Ditzel T K. Chronic interstitial enteritis. *Brit M J* 2 1068 1070 1913
- 16 Felsen J and Gorenberg H. Chronic dysentery: distal ileitis and ulcerative colitis: a follow up of the Jersey City epidemic of bacillary dysentery. *Am J M Sc* 192 553 556 1936
- 17 Rosenthal H. Die Darmbefunde bei der einheimischen Sprue. *Virchows Arch f path Anat* 298 706 727 1937
- 18 Dixon C F. Regional enteritis. *Ann Surg* 108 857 866 1938
- 19 Crohn B B. Regional ileitis. *Surg Gynec & Obst* 68 314 321 1939
- 20 Mixer C G. Regional enteritis. *Surg Gynec & Obst* 68 322 326 1939
- 21 Moschowitz F. Terminal ileitis: clinical recovery without operation four years after onset. *J Mt Sinai Hosp* 7 77 80 1940
- 22 Rhoads J E. The management of regional ileitis and other ulcerative lesions of the intestines. *Pennsylvania M J* 42 1030 1053 1939
- 23 Albright F and Stewart J D. Hypovitaminosis of all fat soluble vitamins due to steatorrhea: report of a case. *New Eng J Med* 223 239 241 1940

## COLLES'S FRACTURE\*

WILLIAM DARRACH, M.D.†

NEW YORK CITY

**A** WORKING knowledge of Colles's fracture is essential because the injury is frequent and is often followed by impaired use of the hand and wrist. This fracture is usually caused by a fall on the outstretched hand.

*Anatomy*

The expanded lower end of the radius articulates with the carpal navicular and lunate below and with the ulnar head on the inner side. The head of the ulna is held against the sigmoid cavity of the radius by the pronator quadratus muscle and by the meniscus. The latter is attached to the lower margin of the sigmoid cavity and the base of the ulnar styloid. In addition, the two collateral ligaments are of importance in stabilizing the wrist. The lower radioulnar ligaments are taut only in the extremes of rotation, and the palmar and dorsal radiocarpal ligaments in extremes of flexion and extension.

Lying in close relation to the lower radius are the various tendons passing from the forearm to the wrist and hand. These tendons and the median nerve are liable either to laceration or to adhesions following the hemorrhage and edema that frequently accompany these fractures.

*Pathology*

*Radius.* The plane of fracture of the radius may be horizontal or oblique, single or comminuted. The whole lower extremity is sometimes shattered, with involvement of the lower articular surface. The commonest type of comminution is that of the dorsal surface. The details of the planes of fractures are significant from the standpoint of maintenance of reduction. After the patient has recovered from the anesthetic, the pull of the flexor and extensor muscles crowds the fragments together. If the plane of fracture is single and horizontal, this force aids in holding the fragments in place, but if it is oblique or comminuted the tendency is for the previous deformity to recur in spite of splints. In adolescents, the bone is apt to give way at the epiphyseal plate.

If displacement is present, the lower fragment may be shifted or tilted. In the former event, its axis remains parallel to that of the upper fragment; in the latter, it is angulated. Such displacement may occur in one of four directions: palmar, dorsal, radial or ulnar. Since the bone is

cancellous, there is apt to be some crushing or impaction. Overriding rarely occurs. The most frequent condition found is a combination of dorsal shift and tilt and radial shift and impaction.

*Ulna.* In the majority of cases with displacement, the ulnar styloid is detached near its base because of the pull of the ulnar collateral ligament. Although it usually heals by fibrous rather than by bony union, this lesion is not serious.

*Inferior radioulnar joint.* This joint is intimately associated with pronation and supination, and its derangement may result in persistent pain or limitation of motion. With any shortening of the radius, the articular surfaces lose their proper relations. The meniscus is often torn. Rarely, an actual dislocation at this joint complicates the fracture.

*Adjacent soft parts.* With a backward displacement of an oblique fracture, the sharp jagged edge of the upper fragment can cause considerable damage to the lower fibers of the pronator quadratus muscle, the flexor tendons and even the median nerve. Rarely, the ulnar nerve may be injured. Injury to the short thumb extensors may result in subsequent rupture.

*Associated injuries.* Fracture of the navicular and luxation of the lunate are sometimes associated injuries.

*Symptoms and Signs*

The symptoms of the break are pain, which may be very mild at first, and weakness of the hand and wrist. Localized tenderness over the line of fracture can be elicited both directly and indirectly. If the patient is seen within a few minutes of injury, a narrow, sharply elevated transverse swelling will be noted on the dorsal surface at the site of fracture, because of hemorrhage. As the blood extravasates and edema ensues, the swelling extends and becomes less prominent. With the usual dorsal and radial shift of the lower fragment, the typical silver-fork deformity occurs. The normally flat dorsal surface of the lower forearm, wrist and hand then shows a distinct elevation. At the same time, the palmar concavity disappears. With any shortening of the radius, the relation of the two styloids is altered. Instead of being almost a centimeter lower, the radial styloid will be nearer the level of the ulnar. Normally, a line passing down the middle of the forearm follows the middle metacarpal and the middle finger. With a radial shift of the lower

\*Presented before the New England Postgraduate Assembly, Cambridge, Massachusetts, October 30, 1941.

†Professor of clinical surgery, Columbia University College of Physicians and Surgeons, attending surgeon, Fracture Service, Presbyterian Hospital.

fragment, this line tends to follow the fourth metacarpal and ring finger. At the same time, the ulnar head becomes more prominent.

### Examination

Examination should be made as gently as possible. With the story of a fall followed by pain and impairment of function, one should presume that a fracture exists until one can prove the contrary. Localized tenderness increases the probability. Actual deformity confirms the diagnosis of fracture with displacement. After a test for possible nerve injury, the examination is completed by x-ray films taken in two planes. In studying x-ray films, it is not enough to establish the primary diagnosis; other bone lesions should be looked for. The main problem, however, is to decide how the planes of fracture run and what displacement exists. Such evidence is needed to decide what maneuvers are necessary to reduce the displacement, what is required to maintain the reduction, how long immobilization is necessary and, lastly, what the probable outcome will be.

### Treatment

**Reduction.** Any displacement of fragments should be corrected except under certain conditions. This requires an anesthetic, either local or general, not only to lessen pain but to reduce the amount of secondary trauma. All materials for immobilization should be assembled before the anesthetic is given. The essential principle in reduction of displacements is to disengage the fragments before trying to manipulate the lower one into place. This is accomplished by traction on the hand, countertraction being applied to the upper arm by an assistant or broad band fastened to the end of the table and the elbow being flexed to a right angle. Traction should be slow and gentle at first and gradually increased as necessary, aided perhaps by rocking of the lower fragment. After the fragments have been disengaged, the lower one can be swung and pushed into place. The exact maneuvers necessary should be planned according to the x-ray evidence. After reduction, the position should be checked under the fluoroscope.

**Immobilization.** The type of splint varies with the habits and desires of the surgeon. Some form of molded plaster splint is perhaps the favorite. I prefer the so-called "sugar-tong" splint, a single strip of plaster that starts in the palm opposite the metacarpal necks, passes up the palmar aspect of the forearm around the flexed elbow and down the dorsal aspect to the metacarpal heads. It is essential to allow free motion at the metacarpophalangeal and interphalangeal joints. As soon as the plaster has set and a bandage has been applied,

post-reduction films should be taken, not only for the surgeon's information but also for his protection. After the swelling has subsided for seven to ten days, it may be wise to change to a circular plaster gauntlet from the midpalm to the upper forearm.

Too early removal of splints tends to prolong rather than shorten convalescence. If the splints allow free motion at the metacarpophalangeal and interphalangeal joints and the patient is made to keep his fingers moving, this not only will maintain range and power in these joints but by internal massage will help the circulation at the site of fracture and thus hasten union.

**Treatment of different types.** From the standpoint of treatment and prognosis, fractures of the lower radius can be divided into four main groups, with three minor types.

**Fractures without displacement**, of course, require no reduction and no anesthetic. After three or four weeks, the splints may be replaced by a leather wristlet. In such fractures, the patient should have complete return of function.

When *fractures with a single horizontal plane of fracture and slight or no impaction* are seen early, complete reduction should be possible. The muscle pull tends to hold the fragments in place, and the wrist can be put in a comfortable mid-position. The period of immobilization needed is but little longer than that in the first group.

When *the plane of fracture is oblique* or when *there is comminution of the dorsal surface*, there is a strong tendency, because of the muscle pull, for the dorsal shift and tilt to recur. This can be partially overcome if the splint is applied with the wrist in strong flexion and moderate adduction. The position can be changed to a more comfortable one during the third week, but splints should be retained for five or six weeks.

There is a group of cases, perhaps 5 per cent, in which *the comminution is so extensive that no form of splint alone prevents collapse and shortening*. In this type, it is well worth while to use the double Kirschner wire and plaster method. One wire is passed through the second, third and fourth metacarpals near their base (the fifth is usually missed). A second wire is inserted higher in the forearm. At first, I used this wire through the radius a little above the middle, but experience has shown that it is better to place it in the upper ulna just distal to the coronoid. After the wires are in place and yoked, reduction is obtained by traction on the wires, with necessary molding. While this is held, a circular plaster is applied, incorporating the two wires. These are left in place for five to seven weeks.

In *very old patients*, it is often wiser to provide protection for a short period without reduction, active motion being started as soon as possible.

Occasionally, *loose fragments* of bone are displaced so as to lie amid the tendons either in front or behind. These should be removed as soon as union has become fairly firm.

Three types of *late disability* can be helped by operative treatment: in cases with persistent posterior shifting of the lower fragment, in which the flexor tendons rub against the sharp edge of the upper fragment, with marked interference with the handgrip, simple removal of the projection through a lateral approach restores the power;

when there is derangement of the lower radio-ulnar joint from shortening of the radius, which interferes with rotation, the pain, disability and deformity of the prominent ulnar head can be relieved by a subperiosteal resection of the lower 2 cm. of the ulna; and in cases with marked dorsal tilt and shift requiring an osteotomy, as the lower fragment is swung forward into position, a triangular space is left that can be filled with the new callus from the dorsal surface—if the ulnar head needs resection, this bone can also be used to fill the vacancy.

184 Washington Avenue

## THE PHARMACODYNAMICS OF SULFADIAZINE IN MAN\*

HERMAN D. RATISH, B.S.,† NATHAN H. SHACKMAN, M.D.,‡ AND JESSE G. M. BULLOWA, M.D.§

NEW YORK CITY

**S**ULFADIAZINE, an analogue of sulfapyridine, (2-sulfanilamido-pyrimidine) has recently been synthesized by Roblin and his associates.<sup>1</sup> Reports on its fate, mode of action, absorption and toxicity in animals<sup>2,3</sup> and in man<sup>4-7</sup> have appeared. The present discussion deals with observations on its pharmacodynamics in man.

### MATERIALS AND METHODS

Ninety-eight men with upper respiratory infections or convalescing from pneumonia were studied. The drug¶ was given orally, intravenously, subcutaneously, intramuscularly and rectally. Observations were made on the fate of single oral doses of 2, 3, and 5 gm. and with repeated doses of 1 gm. every four and every six hours. Intravenously, 5 gm. of sodium sulfadiazine dissolved in 50 cc. of sterile distilled water was injected within one to three minutes. Infusions of 500 or 1000 cc. of a 0.5 or 1.0 per cent solution of sodium sulfadiazine in sterile physiologic saline were given at the rate of 2.5 to 3.0 cc. per minute. Subcutaneously, 1000 cc. of a 0.5 per cent solution of sodium sulfadiazine in saline was administered over a period of two hours. Intramuscularly, 2 or 3 gm. of sodium sulfadiazine in 50 cc. of sterile distilled water was injected into the upper outer quadrant of the buttocks. Rectally, 5 gm. of sulfa-

diazine was given as a retention enema (starch). Determinations of free and total sulfadiazine in the blood were made at intervals of fifteen minutes for the first hour, at hourly intervals for the next five hours and at intervals of twenty-four hours until the blood showed negligible amounts. Collection and analysis of urine were continued until only traces were detected. The distribution of the drug was studied in the spinal, pleural and peritoneal fluids. The concentrations were determined by the method of Bratton and Marshall<sup>8</sup> by means of a photoelectric colorimeter.

### ABSORPTION FROM GASTROINTESTINAL TRACT

#### Oral Administration

The sulfadiazine concentrations in the blood obtained after single oral doses of 2, 3 and 5 gm. are shown in Figure 1. At the end of four hours, single 2-gm. doses of sulfadiazine in 5 subjects resulted in blood levels of the free drug ranging from 2.0 to 3.5 mg. per 100 cc. Single 3-gm. doses given to 6 subjects yielded blood levels varying from 2.5 to 4.0 mg. per 100 cc. Seven subjects who received 5-gm. doses had concentrations of free sulfadiazine ranging from 3.6 to 5.5 mg. per 100 cc. In all cases, measurable quantities of the drug were found in the blood for seventy-two hours.

Multiple oral doses of sulfadiazine were administered to 40 subjects to determine and evaluate the blood concentrations obtainable with different dosage schedules. When statim doses of 2, 3, 4 and 5 gm. were followed by 1 gm. every four or six hours, day and night, it was found that those subjects who had received 4 or 5 gm. as an initial dose maintained slightly higher levels

\*From the Medical Service, Harlem Hospital, Department of Hospitals, New York City, and the Littauer Pneumonia Research Fund of New York University College of Medicine.

†This study received additional financial support from the Metropolitan Life Insurance Company, New York City, and from Mr. Bernard M. Baruch, Mr. Bernard M. Baruch, Jr., Miss Belle N. Baruch and Mrs. H. Robert Samstag.

‡Chemist, Littauer Pneumonia Research Fund.

§Littauer Fellow in Pneumonia Research, Harlem Hospital.

¶Clinical professor of medicine, New York University College of Medicine; visiting physician, Harlem Hospital; visiting physician, Willard Parker Hospital.

¶We are indebted to Dr. W. G. Malcolm, of Lederle Laboratories, Incorporated, Pearl River, New York, for generous supplies of sulfadiazine and sodium sulfadiazine.

than those who had received the smaller doses. The levels, however, were maintained as well when the continued doses were given at intervals of four or six hours.

### Rectal Administration

Following a retention enema containing 5 gm of sulfadiazine, the concentration in the blood

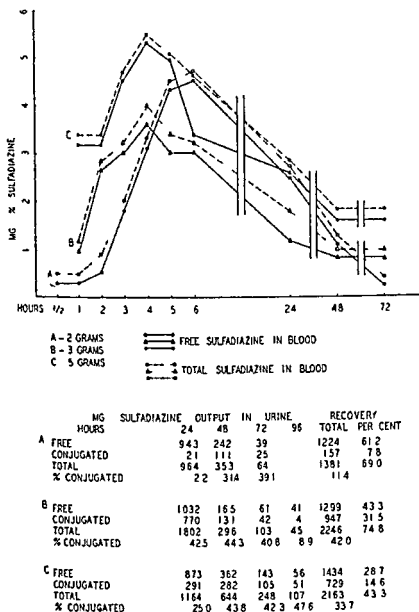


FIGURE 1 Sulfadiazine (Free and Total) Blood Concentrations and Urinary Excretions after Single Oral Doses of 2 (A), 3 (B) and 5 (C) Gm of Sulfadiazine

was never above 10 mg. per 100 cc, but traces were detectable for seventy two hours

### PARENTERAL ADMINISTRATION

Parenteral administration may be advisable because some patients cannot take the drug orally or an early high concentration is required. The available routes are intravenous, subcutaneous and intramuscular.

### Intravenous Route

High concentrations were found immediately in all subjects receiving sodium sulfadiazine intravenously. Free sulfadiazine in the blood reached concentration peaks varying from 16 to 24 mg per 100 cc in ten to thirty minutes after injection of 5 gm of the drug. The blood concentrations

decreased gradually for the first six hours. This was followed by a more rapid decline for the next eighteen hours, and traces were detectable after forty eight hours.

Because of the rapid drop in concentration following intravenous injection of the drug, an attempt was made to maintain high levels with a continuous slow infusion. A series of 8 subjects received infusions of 500 to 1000 cc of a 0.5 or 1.0 per cent solution of sodium sulfadiazine at the rate of 2.5 to 3.0 cc per minute. During the infusion, a steady increase in concentration occurred. Peaks ranged from 11.9 to 19.2 mg of free sulfadiazine per 100 cc. The decline in concentration following the cessation of the infusion, although steep, was not so sharp as that following a rapid injection of the same amount of drug in greater

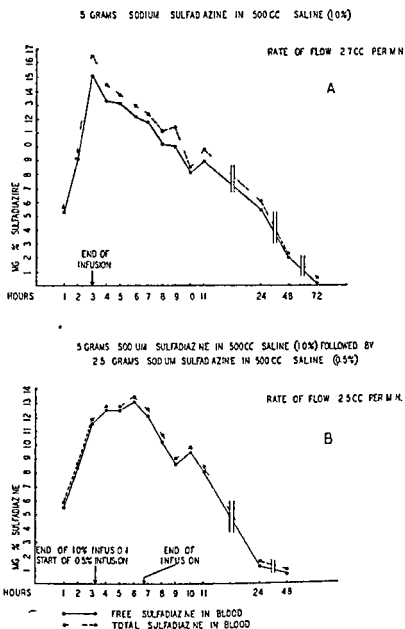


FIGURE 2 Sulfadiazine (Free and Total) Blood Concentrations (A and B), after Continuous Intravenous Infusion of Sodium Sulfadiazine, Using Solutions of Different Strengths

concentrations. Figure 2 shows representative curves.

In 1 subject, an initial infusion of 5 gm of the sodium salt of the drug in 500 cc. of physiologic saline solution produced a blood concentration of



zine. Gross hematuria occurred on three occasions. In no case did albumin or casts appear in the urine as a result of the drug. Neither intramuscular nor subcutaneous injections produced

ment of the concentration of the infusion liquid or by regulation of the rate of flow. Although the immediate levels obtained with the slow infusion method are somewhat lower than those

TABLE 2. *Relation of Free Sulfadiazine Concentrations in Spinal, Pleural and Peritoneal Fluids to Simultaneous Blood Levels.*

PATIENT	DAY OF TREATMENT	TOTAL DOSE gm.	ROUTE OF ADMINISTRATION	TYPE OF FLUID	CONCENTRATION OF FREE SULFADIAZINE			DIAGNOSIS
					BLOOD LEVEL mg./100 cc.	FLUID LEVEL mg./100 cc.	PERCENTAGE OF BLOOD LEVEL	
M. B.	4	20	Intravenous	Spinal	33.6	22.6	67	Meningitis (pneumococcus, Type 14)
M. L.	3	10	Oral	Spinal	16.2	10.3	63	Meningococcal meningitis
	4	14		Spinal	16.2	9.1	56	
	5	20		Spinal	15.3	9.4	61	
	6	28.5		Spinal	17.6	11.4	65	
	9	53		Spinal	14.4	8.6	60	
J. S.	2	10	Oral	Spinal	6.7	4.2	63	Tuberculous meningitis
	4	18		Spinal	5.5	3.9	71	
F. J.	5	50	Intravenous and oral	Spinal	25.0	21.5	86	Meningitis (pneumococcus, Type 8)
D. S.	6	29	Oral	Spinal	7.3	6.6	90	Pneumonia (pneumococcus, Type 7)
R. L.	6	68	Intravenous and oral	Spinal	18.4	15.8	86	Meningitis (pneumococcus, Type 3)
	9	119		Spinal	28.2	23.0	81	
	10	119		Spinal	12.4	11.8	95	
J. W.	4	71	Intravenous and oral	Spinal	25.8	15.2	59	Meningitis (pneumococcus, Type 7)
	5	106		Spinal	27.8	20.6	74	
	8	202		Spinal	52.4	33.6	64	
E. J.	2	25	Oral	Spinal	28.8	24.2	84	Meningococcal meningitis
R. A.	4	20	Oral	Pleural	11.1	6.0	54	Lung abscess with empyema
C. F.	4	18	Oral	Pleural	2.9	1.9	65	Pneumonia (pneumococcus, Type 7) with sterile effusion
H. D.	4	23	Oral	Pleural	5.3	7.0	132	Pneumonia (pneumococcus, Type 7) with sterile effusion
S. N.	5	26	Oral	Pleural	5.7	6.5	114	Pneumonia (pneumococcus, Type 2) with sterile effusion
E. B.	4	21	Oral	Pleural	7.3	6.0	82	Lung abscess with empyema
L. W.	4	25	Oral	Pleural	13.6	15.3	112	Pneumonia (pneumococcus, Type 3) with sterile effusion
A. W.	7	43	Oral	Pleural	8.7	10.5	121	Empyema (pneumococcus, Type 7)
A. P.	1	5	Intravenous	Ascitic	15.2	21.2	140	Cirrhosis of liver

any adverse local or general reactions. The high pH (9.5) of the solutions was apparently without harmful effects.

### DISCUSSION

Sulfadiazine is readily absorbed from the gastrointestinal tract. Blood concentrations obtained are generally higher than those observed with similar doses of sulfapyridine and sulfathiazole. The drug disappears from the blood more slowly than either of these. The amount conjugated in the blood is less than that with sulfapyridine or sulfathiazole. The conjugated fraction in blood and urine does not increase with continued administration. In the urine, about a third is found to be conjugated, although in exceptional cases a much larger proportion may be excreted in this form. Rapid urinary excretion of the drug may account for the small quantities of conjugated sulfadiazine in the blood.

When both rapid attainment and maintenance of high blood levels are desirable and oral administration is not feasible, the intravenous infusion of sodium sulfadiazine is practical. Blood concentration may be varied either by adjust-

tained with the rapid intravenous injection of similar dose, a high concentration is more readily maintained. This method is safe, flexible and efficacious.

Sulfadiazine is widely and readily distributed in body fluids. It penetrates well into the pleural and peritoneal cavities. Concentrations in the spinal fluid are usually about two thirds those of the simultaneous blood levels.

With initial doses of 2, 3, 4 and 5 gm. followed by 1 gm. every six hours, levels are obtained that are similar to those reached when the drug is given every four hours. Blood concentrations are independent of the total dose and the dose per kilogram of body weight.

The incidence of toxic reactions is less with sulfadiazine than with sulfapyridine and sulfathiazole. When reactions occur, they are mild.

### CONCLUSIONS

Sulfadiazine is readily absorbed from the gastrointestinal tract.

High levels may be obtained by several routes but a rapid attainment and maintenance of high

than those who had received the smaller doses. The levels, however, were maintained as well when the continued doses were given at intervals of four or six hours.

### Rectal Administration

Following a retention enema containing 5 gm of sulfadiazine, the concentration in the blood

decreased gradually for the first six hours. This was followed by a more rapid decline for the next eighteen hours, and traces were detectable after forty eight hours.

Because of the rapid drop in concentration following intravenous injection of the drug, an attempt was made to maintain high levels with a continuous slow infusion. A series of 8 subjects received infusions of 500 to 1000 cc of a 0.5 or 1.0 per cent solution of sodium sulfadiazine at the rate of 25 to 30 cc per minute. During the infusion, a steady increase in concentration occurred. Peaks ranged from 11.9 to 19.2 mg of free sulfadiazine per 100 cc. The decline in concentration following the cessation of the infusion, although steep, was not so sharp as that following a rapid injection of the same amount of drug in greater

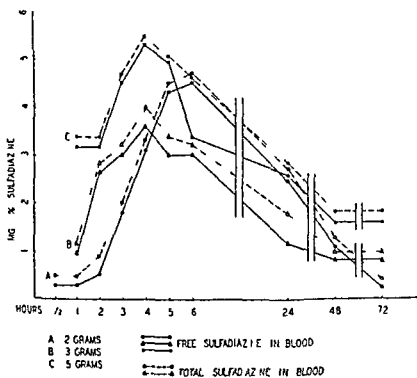


FIGURE 1 Sulfadiazine (Free and Total) Blood Concentrations and Urinary Excretions after Single Oral Doses of 2 (A), 3 (B) and 5 (C) Gm of Sulfadiazine

was never above 10 mg per 100 cc, but traces were detectable for seventy two hours.

### PARENTERAL ADMINISTRATION

Parenteral administration may be advisable because some patients cannot take the drug orally or an early high concentration is required. The available routes are intravenous, subcutaneous and intramuscular.

### Intravenous Route

High concentrations were found immediately in all subjects receiving sodium sulfadiazine intravenously. Free sulfadiazine in the blood reached concentration peaks varying from 16 to 24 mg per 100 cc in ten to thirty minutes after injection of 5 gm of the drug. The blood concentrations

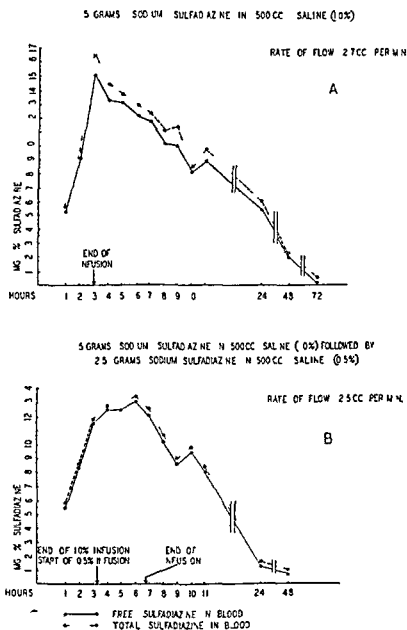


FIGURE 2 Sulfadiazine (Free and Total) Blood Concentrations (A and B) after Continuous Intravenous Infusion of Sodium Sulfadiazine, Using Solutions of Different Strengths

concentrations. Figure 2 shows representative curves.

In 1 subject, an initial infusion of 5 gm of the sodium salt of the drug in 500 cc of physiologic saline solution produced a blood concentration of

11.5 mg. per 100 cc. at the termination of the infusion (Fig. 2B). When this was immediately followed by 500 cc. of a 0.5 per cent solution at the same rate of flow, blood levels between 12 and 13 mg. per 100 cc. were maintained for the duration of the infusion (four hours). In another case, the initial infusion of 5 gm. sodium sulfadiazine in 1000 cc. of saline solution was followed by oral doses of 0.5 gm. every four hours. Concentrations between 9 and 11 mg. per 100 cc. were maintained.

### Subcutaneous Route

Three subjects received 5 gm. of sodium sulfadiazine subcutaneously in 1000 cc. of physiologic saline solution; the hypodermoclysis required two hours. The highest concentration of the free sulfadiazine was reached in six hours, the peaks being 7.5, 7.8 and 8.2 mg. per 100 cc. respectively (Figure 3). The increase, as well as the drop, in

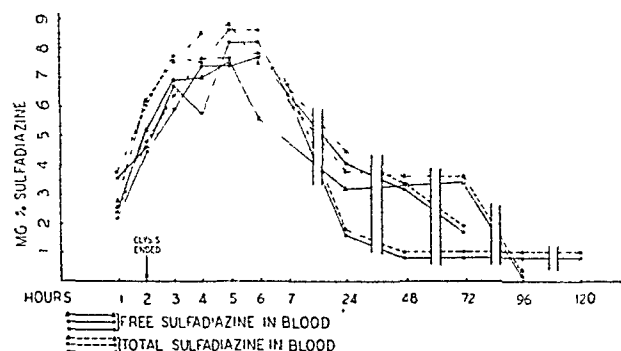


FIGURE 3. *Sulfadiazine (Free and Total) Blood Concentrations Following Hypodermoclysis of 5 Gm. of Sodium Sulfadiazine in 1000 Cc. Saline Solution in 3 Patients.*

concentration was gradual, and in one subject a concentration of 1.0 mg. per 100 cc. was detectable at the end of one hundred and twenty hours.

### Intramuscular Route

Two subjects were given 2 and 3 gm. of sodium sulfadiazine (in 50 cc. of sterile distilled water) intramuscularly in one minute. The pH of the solution was 9.5. The blood levels reached peaks of 6.2 and 8.5 mg. of free sulfadiazine per 100 cc., respectively, in one hour and dropped gradually (Fig. 4). The blood-level curves show a similarity to those obtained after intravenous injection.

### CONJUGATION IN BLOOD

Conjugated sulfadiazine is present in small amounts in the blood. Different subjects showed only moderate variations in the quantity of conjugated sulfadiazine, and the quantities were small irrespective of the amount administered or its portal.

In 1 case, the conjugated sulfadiazine in the blood was markedly elevated. This patient was given a single dose of 5 gm. of sulfadiazine orally. Concentrations of the free and conjugated drug

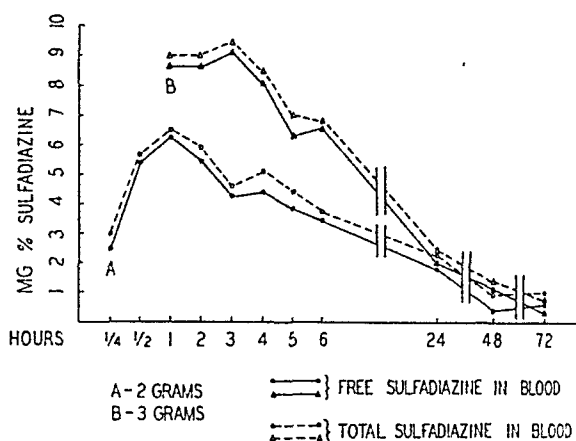


FIGURE 4. *Sulfadiazine (Free and Total) Blood Concentrations Resulting from Intramuscular Injections of 2 (A) and 3 (B) Gm. of Sodium Sulfadiazine in Distilled Water.*

were detectable seven days after it had been administered. At the end of ninety-six hours, the blood contained 5.3 mg. of the conjugated form per 100 cc. and 2.3 mg. of the free form. The urine in this case also showed an unusual output of conjugated sulfadiazine. The total recovery was 61.8 per cent, two thirds of which was conjugated. This subject had nephrosclerosis with azotemia (a blood creatinine of 6.0 and a blood urea nitrogen of 130 mg. per 100 cc.).

### ELIMINATION

Discontinuance of administration is followed by early rapid excretion, which subsequently becomes slower. Sulfadiazine was observed in the urine within thirty minutes after oral administration, and immediately after intravenous injection. Within seventy-two hours, most of it had been eliminated. Approximately 50 per cent of the total amount recovered was excreted in the first twenty-four hours, and about 80 per cent in forty-eight hours. For as long as six days, both free and conjugated forms could be detected in measurable quantities in the urine.

The amount of sulfadiazine (free and conjugated) recovered from the urine varied from 30.4 to 94.5 per cent of the dose given, with an average of 60.5 per cent (Table 1). After oral administration, the recovery averaged 56.1 per cent, and after intravenous, intramuscular and subcutaneous administration, the average recovery was 69.7 per cent.

Generally, there was a lag of twenty-four hours in the appearance in the urine of the conjugated as compared with the free form. In most cases,

of the total amount recovered in the urine, about 35 per cent was excreted as conjugated sulfadiazine, with extremes of 11.4 and 71.4 per cent. Of the total amount of conjugated drug recovered, approximately 45 per cent was accounted for in the first twenty-four hours, and 75 per cent in the first forty-eight hours. The percentage of conjugated sulfadiazine excreted from day to day was

free drug was 21.3 mg. per 100 cc., as compared with 15.2 mg. in the blood.

#### DISTRIBUTION BETWEEN CELLS AND PLASMA

Several blood samples, at hourly intervals, were drawn from each of 6 subjects to study the distribution of the drug in blood cells and plasma. Approximately 80 per cent of the sulfadiazine was

TABLE 1. *Urinary Recovery of Sulfadiazine.*

PATIENT	ROUTE OF ADMINISTRATION	DOSE	AMOUNT RECOVERED			PERCENTAGE CONJUGATED (OF TOTAL RECOVERY)	PERCENTAGE RECOVERED		
			FREE	CONJUGATED	TOTAL		FREE	CONJUGATED	TOTAL
		gm	mg	mg	mg				
C. F.	Oral	2	1224	157	1381	11.4	61.2	7.8	69.0
G. A.	Oral	2	1242	609	1901	12.0	14.1	30.4	44.5
A. S.	Oral	3	442	1105	1547	71.4	14.7	36.8	51.5
J. B.	Oral	3	58	450	1208	37.2	25.2	15.0	40.2
C. F.	Oral	3	705	205	913	22.4	23.6	6.8	30.4
W. J.	Oral	3	1258	947	2245	42.2	43.3	31.6	74.9
T. H.	Oral	5	12.4	972	2246	43.3	25.5	19.5	45.0
C. F.	Oral	5	17.8	700	2478	28.3	35.5	14.0	49.5
O. S.	Oral	5	10.6	2087	3093	67.4	20.1	41.8	61.9
D. D.	Oral	5	204	1087	1313	34.7	40.9	21.7	62.6
G. E.	Oral	5	1434	729	2163	33.7	28.7	14.6	43.3
A. M.	Oral	11*	3701	1494	5195	28.7	33.7	13.6	47.3
M. C.	Oral	14*	5812	4783	10,595	45.1	41.5	34.2	75.7
W. B.	Oral	22*	2546	5673	8219	69.0	11.6	25.8	37.4
R. T.	Intravenous	5†	18.3	497	2370	20.9	37.5	9.9	47.4
H. S.	Intravenous	5†	2294	894	3098	25.8	45.9	16.1	62.0
B. D.	Intravenous	2†	3415	896	4311	20.8	45.7	11.9	57.6
A. F.	Intramuscular	3†	1087	316	1405	22.5	54.4	15.8	70.2
F. H.	Intramuscular	3†	1918	878	2796	31.4	63.9	29.3	93.2
B. D.	Subcutaneous	5†	3038	1138	4176	27.2	60.7	22.8	83.5
A. W.	Subcutaneous	5†	2448	1241	3689	33.6	48.9	24.9	73.8

\*Repeated doses

†Sodium sulfadiazine

approximately the same in all patients, irrespective of the duration of administration (Fig. 1). It appears that the rate of conjugation, as measured by urinary excretion, is a characteristic of the patient and does not depend on the amount of drug given or its route of administration.

#### DISTRIBUTION IN BODY FLUIDS

The drug may be detected in high concentrations in the spinal, pleural and peritoneal fluids. As indicated in Table 2, the spinal-fluid levels of free sulfadiazine varied from 56 to 95 per cent of the simultaneous blood levels. In some cases (M. L., R. L. and J. W.), a tendency to maintain a fairly constant relation to the blood levels was observed. In pleural fluid, collected without local anesthesia, the range was 54 to 132 per cent of the blood levels. In none of these, had the drug been injected into the pleural space. The possibility that the excretion of the drug from the pleural fluid into the blood is slower than its absorption from the blood is a probable explanation for the high pleural-fluid concentrations. In one subject (A. P.), following an intravenous injection of 5 gm. of sodium sulfadiazine, a concentration of 8 mg. of the free drug per 100 cc. was observed in the ascitic fluid in ten minutes. At the end of forty minutes, the concentration of the

found in the plasma. There was no relation between the distribution and blood levels. The amounts of conjugated sulfadiazine were small in both cells and plasma.

#### SOLUBILITY

Sulfadiazine was found to vary in solubility with the medium employed. When the solubility of the drug was tested at 22°C. and at 37°C., it was found to be 9 and 12 mg. per 100 cc., respectively, in water, 13 and 19 mg. per 100 cc. in physiologic saline solution, and 136 and 204 mg. per 100 cc. in whole blood. In serum, at 22°C., it was soluble to the extent of 206 mg. per 100 cc.

#### TOXICITY

In the subjects reported herein and in a larger series (over 300 cases) to be reported, the incidence of toxic manifestations was relatively low. Nausea and vomiting occurred in 10 per cent of the cases. A morbilliform rash was seen in 3 patients, 1 of whom also had a moderately severe conjunctivitis. Blood changes and mental disturbances were not encountered. Crystals in the urine were less frequently observed than with the other drugs. In 1 case, at operation, crystals of sulfadiazine were present in the pleural fluid following an intrapleural injection of a solution of sodium sulfadiazine.

zine. Gross hematuria occurred on three occasions. In no case did albumin or casts appear in the urine as a result of the drug. Neither intramuscular nor subcutaneous injections produced

ment of the concentration of the infusion liquid or by regulation of the rate of flow. Although the immediate levels obtained with the slow infusion method are somewhat lower than those ob

TABLE 2. *Relation of Free Sulfadiazine Concentrations in Spinal, Pleural and Peritoneal Fluids to Simultaneous Blood Levels.*

PATIENT	DAY OF TREATMENT	TOTAL DOSE	ROUTE OF ADMINISTRATION	TYPE OF FLUID	CONCENTRATION OF FREE SULFADIAZINE			DIAGNOSIS
					BLOOD LEVEL	FLUID LEVEL	PERCENTAGE OF BLOOD LEVEL	
					mg./100 cc.	mg./100 cc.		
M. B.	4	20	Intravenous	Spinal	33.6	22.6	67	Meningitis (pneumococcus, Type 14)
M. L.	3	10	Oral	Spinal	16.2	10.3	63	Meningococcal meningitis
	4	14		Spinal	16.2	9.1	56	
	5	20		Spinal	15.3	9.4	61	
	6	28.5		Spinal	17.6	11.4	65	
	9	53		Spinal	14.4	8.6	60	
J. S.	2	10	Oral	Spinal	6.7	4.2	63	Tuberculous meningitis
	4	18		Spinal	5.5	3.9	71	
F. J.	5	50	Intravenous and oral	Spinal	25.0	21.5	86	Meningitis (pneumococcus, Type 8)
D. S.	6	29	Oral	Spinal	7.3	6.6	90	Pneumonia (pneumococcus, Type 7)
R. L.	6	68	Intravenous and oral	Spinal	18.4	15.8	86	Meningitis (pneumococcus, Type 3)
	9	119		Spinal	28.2	23.0	81	
	10	119		Spinal	12.4	11.8	95	
J. W.	4	71	Intravenous and oral	Spinal	25.8	15.2	59	Meningitis (pneumococcus, Type 7)
	5	106		Spinal	27.8	20.6	74	
	8	202		Spinal	52.4	33.6	64	
E. J.	2	25	Oral	Spinal	28.8	24.2	84	Meningococcal meningitis
R. A.	4	20	Oral	Pleural	11.1	6.0	54	Lung abscess with empyema
C. F.	4	18	Oral	Pleural	2.9	1.9	65	Pneumonia (pneumococcus, Type 7) with sterile effusion
H. D.	4	23	Oral	Pleural	5.3	7.0	132	Pneumonia (pneumococcus, Type 7) with sterile effusion
S. N.	5	26	Oral	Pleural	5.7	6.5	114	Pneumonia (pneumococcus, Type 2) with sterile effusion
E. B.	4	21	Oral	Pleural	7.3	6.0	82	Lung abscess with empyema
L. W.	4	25	Oral	Pleural	13.6	15.3	112	Pneumonia (pneumococcus, Type 3) with sterile effusion
A. W.	7	43	Oral	Pleural	8.7	10.5	121	Empyema (pneumococcus, Type 7)
A. P.	1	5	Intravenous	Ascitic	15.2	21.2	140	Cirrhosis of liver

any adverse local or general reactions. The high pH (9.5) of the solutions was apparently without harmful effects.

DISCUSSION

Sulfadiazine is readily absorbed from the gastrointestinal tract. Blood concentrations obtained are generally higher than those observed with similar doses of sulfapyridine and sulfathiazole. The drug disappears from the blood more slowly than either of these. The amount conjugated in the blood is less than that with sulfapyridine or sulfathiazole. The conjugated fraction in blood and urine does not increase with continued administration. In the urine, about a third is found to be conjugated, although in exceptional cases a much larger proportion may be excreted in this form. Rapid urinary excretion of the drug may account for the small quantities of conjugated sulfadiazine in the blood.

When both rapid attainment and maintenance of high blood levels are desirable and oral administration is not feasible, the intravenous infusion of sodium sulfadiazine is practical. Blood concentration may be varied either by adjust-

tained with the rapid intravenous injection of a similar dose, a high concentration is more readily maintained. This method is safe, flexible and efficacious.

Sulfadiazine is widely and readily distributed in body fluids. It penetrates well into the pleural and peritoneal cavities. Concentrations in the spinal fluid are usually about two thirds those of the simultaneous blood levels.

With initial doses of 2, 3, 4 and 5 gm. followed by 1 gm. every six hours, levels are obtained that are similar to those reached when the drug is given every four hours. Blood concentrations are independent of the total dose and the dose per kilogram of body weight.

The incidence of toxic reactions is less with sulfadiazine than with sulfapyridine and sulfathiazole. When reactions occur, they are mild.

CONCLUSIONS.

Sulfadiazine is readily absorbed from the gastrointestinal tract.

High levels may be obtained by several routes but a rapid attainment and maintenance of high

blood levels is best accomplished with continuous slow infusion.

The amount of conjugated sulfadiazine in the blood is small, usually less than 20 per cent

Although the amount of conjugated sulfadiazine excreted in the urine varies in different subjects, approximately 35 per cent is excreted in this form

The drug diffuses well into the body fluids

The ratio of spinal-fluid to blood concentration appears to be constant.

Toxic manifestations of sulfadiazine are less frequent and milder than those noted with sulfapyridine and sulfathiazole.

## REFERENCES

- 1 Rabin R O Jr Williams J H Winick P S, and English J P Chemotherapy, some sulfanilamide heterocycles *J Am Chem Soc* 62:209 2005 1940
- 2 Feinstein W H Williams R D, Wolfe R T, Huntington E and Crossley M L The toxicity absorption, and chemotherapeutic activity of 2 sulfanilamide pyrimidine (sulfadiazine) *Bull Johns Hopkins Hosp* 67:427-456 1949
- 3 Long T H, Bliss E A and Ott E Studies on sulfadiazine *Bull Johns Hopkins Hosp* 69:79 302 1941
- 4 Plummer N and Entwistle H K Absorption and excretion of sulfadiazine *Proc Soc Exper Biol & Med* 45:734 738 1940
- 5 Reichold J G Flippin H F Schwartz L and Domm A H Absorption distribution and excretion of 2 sulfanilamide pyrimidine (sulfapyridine, sulfadiazine) in man *Am J M Sc* 201:106-115 1941
- 6 Peterson O L Strauss E Taylor F H L and Finland M Absorption excretion and distribution of sulfadiazine (2 sulfanilamidopyrimidine) *Am J M Sc* 201:357 367 1941
- 7 Sidusk J F Jr, and Tredway J B Observations on absorption excretion on diffusion and acylation of sulfadiazine in man *Yale J Biol & Med* 13:539 556 1941
- 8 Bratton A C and Marshall L K Jr New coupling component for sulfanilamide determination *J Biol Chem* 128:537 550 1939

## UNUNITED HIP FRACTURES\*

OTTO J HERMANN, MD†

BOSTON

DURING the last decade or so, surgeons have concentrated on the initial reduction, fixation and aftercare of fresh fractures of the femoral neck. As a result, the percentage of good end results typified by solid union and painless functioning has markedly increased. However, as I<sup>1</sup> contended in 1940, when I had occasion to discuss the problem of ununited hip fractures, ununited femoral neck fractures, including many of the nonfunctioning, painful types, still occur. To render the limb painless and functioning, some type of reconstructive (or as the late Dr F J Cotton tersely put it, "destructive") type of operation is required.

### METHODS

Various types of reconstructive procedures for these cases of nonunion have evolved. But I still believe that the following five methods form a good armamentarium for the surgeon attempting to do such work: the Colonna<sup>2</sup> (a modification of the Whitman<sup>3</sup>); the Magnuson<sup>4</sup> (a modification of the Brackett<sup>5</sup>), the various bone stimulating operations—direct grafting, chip grafts, peg grafts and hole drilling, the fusion operation, and the simple oblique McMurray<sup>6</sup> osteotomy method. Since my views on the first four methods have not changed radically during the last two years, I quote below what I had to say of them at that time.

The fifth, the McMurray method, I practically passed over because up to that time my experience with it had been short and unsatisfactory. Since

then, I have done such osteotomies in 8 cases, with gratifying end results in 6. The remaining 2 patients were treated too recently for the ultimate outcome to be judged, all that I can say about them is that to date they are progressing well. My experience with the method during the last two years has impressed me very favorably with its simplicity, its wide adaptability and its promise of a high rate of good end results and of a return to normalcy.

To offer a basis of comparison between methods, I shall review the operative procedure of the first four methods and my evaluation of them, as I gave them in the previous paper, with some very minor revisions. Following this, I shall consider the McMurray oblique osteotomy.

The Colonna type of reconstruction consists in: sectioning close to their insertions of all muscles attached to the region of the greater trochanter, with preservation of a thin layer of fibromuscular tissue over the upper end of the bone; removal of the head; placing of the upper extremity of the femur deeply and firmly within the acetabulum, transplantation of the gluteus medius and minimus group of muscles downward on the shaft of the femur as far as they will reach, and the secure fastening of them to the bone; after wound repair and dressing, application of a plaster-of-Paris spica with the leg in 20 to 30° abduction; at the end of four weeks, cutting away of the lower posterior half of the cast in the affected leg so as to allow knee flexion several times a day; removal of the entire cast in the sixth week, placing of the leg in a special type of foot sling hitched to a Balkan frame, and institution of a special series

\*Read by title at the annual meeting of the New England Surgical Society, Hanover, New Hampshire, September 5, 1941.

†Assistant professor of surgery, Tufts College Medical School, associate in surgery, Harvard Medical School, surgeon-in-chief, Bone and Joint Service, Boston City Hospital.

of exercises; and use of crutches at the eighth week and direct weight bearing one to two weeks, or more, later, depending on the individual case.

The essentials of the Magnuson<sup>4</sup> method (a modification of the Brackett method) are: exposure by the Smith-Petersen or the Callahan approach; removal of fibrous tissues between the fractured ends, followed by a test to ascertain whether the head is viable or nonviable; hollowing of the head in the form of a cone, pointing upward and slightly backward; rotation of the femur inward and, with a thin-bladed chisel, removal of the trochanter in a line sloping from the base of the neck of the shaft; rounding of the end of the shaft in the same curve as that in which the head has been hollowed out; abduction of the leg so that the upper end of the shaft may be pried into the head; reattachment of the trochanter to the shaft on the cut surface so that it is moved downward and outward and held in that position by heavy silk ligatures; application of a plaster-of-Paris spica, which is retained for eight to twelve weeks, occasionally longer in my experience (that is, until bony union has taken place); removal of the spica, the legs being kept in some abduction, however; finally, periodic clinical examinations and check-up roentgenograms to determine when actual direct weight bearing can be started.

The various direct bone-grafting, pegging and hole-drilling methods, I believe, need not be described, since they are so varied. Suffice it to say that when I decide to use such a procedure I combine several. These operations are followed by plaster-of-Paris spica fixation for ten to fourteen weeks, or until union has been established, and then by the use of crutches and protective ambulatory splints until definite firm union has been obtained.

The hip-fusion method is generally performed by means of Hibbs's procedure, or with some modification, when the head of the femur must be removed or is useless. In these cases, Cotton<sup>7</sup> combined Hibbs's fusion operation with Albee's old plan of squaring. Following the operation, a plaster-of-Paris spica is applied and retained until fusion is established. As a rule, this takes twelve to sixteen weeks. A walking spica is then applied, or if fusion is firm, a protective ambulatory splint and crutches or crutches alone are used. No direct weight bearing is permitted until union has been firmly established clinically and roentgenographically.

Dr. Charles H. Bradford,<sup>8</sup> who is with the American Hospital in England, describes a hip-fusion method that is being worked out by Dr.

Britten, who does the equivalent of a McMurray osteotomy, slides the shaft inward and lays a wide solid piece of tibial graft above it like a roof, firmly set in the chiseled groove in the ischium just below the acetabulum. Dr. Bradford considers this type of arthrodesis to be a revolutionary development that may replace all other forms of hip fusion. I mention it because I consider it much simpler and basically sounder than the prevalent hip-fusion methods.

The McMurray<sup>6</sup> osteotomy is a bifurcation operation based on the suggestion of Lorenz<sup>9</sup> in which the shaft of the femur is transferred directly under the lower margin of the acetabulum and head of the femur. The chief purpose of this operation is to change a shearing force into a direct one. The following are the steps in the procedure: a 15-cm. incision is made along the lateral side of the upper end of the femur in the trochanteric area; the fracture site is exposed so as to place the osteotomy line accurately; an oblique osteotomy is performed, beginning on the outer side of the shaft, generally about the lower end of the greater trochanter, and ending above the tip of the lesser trochanter; the upper end of the shaft of the femur is pried and shoved inward until the cut end is under the acetabulum and femoral head—this is followed by repair of the wound; a plaster-of-Paris fixation is used for a period long enough to ensure union at the site of the osteotomy (varying in my cases from eight to fourteen weeks). This fixation of the limb is in the neutral position in very slight abduction, to prevent the development of knock-knee following removal of the plaster cast. McMurray asserts the objection that this protracted fixation by plaster spica is likely to be followed by troublesome rigidity, especially if the knee joint does not hold, since in that event there is no torsion of the limb and consequently no continued strain on the joint, which lies comfortably in neutral, slight flexion position.

McMurray warns that the osteotomy should not be carried out on too high a level because the shaft of the femur cannot then be put under the head and acetabulum. Also, if the osteotomy is done at too low a level, no weight is borne directly through the shaft of the femur, so that the strain at the site of nonunion remains unaltered. The obliquity of the osteotomy makes more certain that union occurs between the fragments. McMurray further stresses the value of the correct position of the transferred shaft under the acetabulum and femoral head, the union between the divided fragments of the femoral shaft and the position of slight abduction, to prevent the development of a subsequent knee deformity.

## RESULTS

Of 12 cases treated by the Colonna method, what may be called good end results were obtained in 8. The patient must be a good operative risk for this procedure. The chronologic age need not be a deterring factor. The patient must, in the surgeon's judgment, be able to withstand a good amount of surgical trauma. The fracture site should show definite absorption of the femoral neck or head; the less femoral neck remaining, the easier the operation and the better the result. This method can also be considered in cases in which the head of the femur is dead. Arthritic changes in the hip are not conducive to a good result with this type of reconstruction, and therefore rule out this operation.

The following facts were noted in the 8 cases treated successfully by the Colonna method. The bed and hospital confinement was shorter than that by any of the other methods used. The average was six weeks in bed; the patients spent another two weeks up and about the ward before discharge. Patients left the hospital under their own power with the aid of a crutch or cane, depending on their confidence and readjustment ability. The average shortening in these cases was less than 2.5 cm.: 1.9 cm. in 3 cases, 2.5 cm. in 4, and 3.8 cm. in 1. This shortening was of no material consequence; it could be corrected by a slightly raised heel. Internal and external rotations at the hip were quite limited; abduction ranged from 25° to 45°, and adduction from 20° to 25°. The flexion at the hip was good, and extension was normal. Patients could stand alone on either leg. They had painless hips and could walk ordinary distances without fatigue or discomfort, although with a slight limp. They had, however, some social and physical discomforts. They complained of inability to put stocking and shoe on the affected leg, and protracted sitting, such as that at the card table or the theater, caused a sense of stiffening and discomfort in the affected hip.

To arrive at this result, the patient must go through a fair amount of severe surgical trauma, but the period of hip and leg fixation is comparatively short, as are bed confinement and hospitalization, which are important items when one knows, as in other procedures, what prolonged fixation and bed treatment will do to a patient locally and generally. This period of immobilization is also a significant factor from an economic standpoint, which today is the concern of both patient and hospital.

Of 7 cases in which the Magnuson operation was employed, good end results were obtained in 4. This method should not be considered in cases

complicated by arthritic changes, or by any suspicion of cartilage degeneration or irregularity, or in cases in which the head of the femur is dead. I also believe that in ununited fractures of over one year's duration, or in cases in which no femoral neck is left, the patients are poor risks for this operation. In my experience, this procedure requires a very careful selection of cases. It involves somewhat more surgical trauma than the Colonna method. The fixation of the hip and leg and the bed confinement were quite long in these cases—ten to sixteen weeks. The patients left the hospital from the end of the tenth to the eighteenth week, under their own power and using crutches or an ambulatory Thomas splint and cane. They were bearing direct weight on the affected hips from the sixth to the ninth month. At that time, there was solid union of the reconstructed neck and head, and the hip joint was 90 per cent and more normal—as nearly normal as one could expect from a reconstruction.

The poor results in 2 cases were unfortunate. Neither fracture united. There was absorption at the reconstructed site soon after the operation. Both patients were over sixty years of age, chronologically and physically. The ununited fractures were of twelve and sixteen months' duration. One of these patients has since died, and the other is up and about as a crutch invalid but has a painless hip.

These cases have caused me to avoid the Magnuson method in ununited fractures of over twelve months' duration and in elderly people. Two of the successful cases were also benefited by these failures in that I not only chose them more carefully but, in addition to the reconstruction, did Bozsán's<sup>10</sup> hole drilling and crammed in some bone chips at the reconstruction site.

Bone grafting and allied methods were employed in 3 cases. The selection of ununited hip fractures for bone grafting, bone chips and hole drilling must be made early and with due care to the general condition of the patients, who must be above average physically to withstand successfully the prolonged spica and bed confinement. The femoral heads should be in good condition, and some of the neck should remain. Here again, those patients with arthritic changes or tendencies, or with any joint irregularity, should not be selected for these procedures.

In the 3 successful cases, the ununited fractures were of six and a half to eight months' duration. The femoral heads were all in good condition, and a fair amount of femoral neck remained. In 1 case, a simple, thorough cleaning out of the fibrous tissue between the head and neck was done, and the resulting gap was crammed



with bone chips. The 2 others had not only the hole drilling, as advocated by Bozsán, but also inlay grafts and bone chips. In these cases, spica fixation was maintained from twelve to sixteen weeks, and hospitalization lasted fourteen to eighteen weeks. All these patients left the hospital wearing protective ambulatory splints and using either a crutch or a cane. The time of direct weight bearing averaged from six to eight months. The knee joints in the affected legs in 2 of these patients lengthened the convalescence and delayed return to normalcy. The third patient had limited knee motion at operation, and this limitation persisted. The hips in the 3 patients had practically normal range of function, which was better than that in the successful Magnuson cases.

The simplicity, ease and nonshocking quality of these allied methods impressed me markedly and made me aware that early recognition of nonunion and early decision to use stimulating therapy should be sought.

The hip-fusion operation was performed in 3 cases. This method has been employed only in those ununited cases in which definite arthritic or other joint changes are shown. Again, my experience is limited, but it has been most satisfactory. Successful end results were obtained in 2 cases, and in another a successful outcome followed a secondary stimulation.

Of course, the successful end result is a stiff hip with social and physical discomforts very similar to those after a good Colonna end result — at least, that is how I have viewed it. To attain this result, the patient must go through severe surgery and a protracted spica fixation and hospitalization, varying from twelve to sixteen weeks. These are serious factors that one must face before selecting such a procedure, which is so tempting because the percentage of failures following its use is lower than that for any of the other present-day methods.

At the Boston City Hospital, 8 ununited hip fractures have been reconstructed by the McMurray osteotomy. Of these, 2 have been done too recently for the result to be judged. Five of the remaining 6 cases have gone to clinically good end results, and 1 patient, although not an absolute failure, still has to use crutches after six months. This simple osteotomy method obviously entails less surgical trauma than the other methods and, hence, less surgical shock. Thus, some cases that are deemed poor surgical risks for the Colonna, Magnuson or fusion operation may qualify for the McMurray method. However, the last is not well adapted to the following types of cases: those in which the femoral head is disintegrating; those in which the femoral neck has been absorbed and

the shaft is riding high; and those in which the nonunion is not too old and the absorption has not progressed too far and in which a simple local bone-stimulating, or the Magnuson, operation seems indicated. Successful end results by these methods give almost 100 per cent return to normalcy and have stood the test of time, which may change some present thoughts on the McMurray osteotomy.

In the few cases done by this method at our hospital, the following data have been gathered: the patients have plaster-of-Paris spica fixation from eight to fourteen weeks, and hospitalization from ten to about seventeen weeks; they generally leave the hospital using crutches but soon thereafter omit them and use only a cane, with a good clinical end result; they still use a cane in going up stairs, limp slightly, but have no local hip pain or tenderness on walking, sitting or lying down; the shortening varies from 2.2 to 2.6 cm.; there is a limited degree of internal, but a good degree of external rotation at the reconstructed hip, and also a good abduction and adduction range; there may be occasional local stiffness; the patients can dress themselves in normal fashion, cross their knees and sit for protracted periods with ease and comfort. In short, a good 80 to 85 per cent return to normalcy is usually obtained.

At present the McMurray osteotomy seems adaptable to a greater variety of the painful ununited femoral-neck fractures than the other methods. The other points in its favor are its simplicity of execution, the production of less surgical shock and, lastly, the fairly high rate of good end results showing a very creditable percentage of return to normalcy.

However, I am still firmly convinced that if an unmistakable diagnosis of nonunion could be made in the early months following the initial reduction and fixation, more of the simple bone-stimulating or Magnuson operations could be performed. I also believe that the Colonna method still has a place in cases in which there has been much degeneration of the head or considerable absorption of the neck, with the shaft consequently riding high.

The fusion operation (possibly of the Britten type) should be reserved for the failures of the other methods and for the markedly arthritic types. I hesitate to do fusion in the very old, because of their extreme slowness to adapt themselves to the limitations of a stiff hip.

\* \* \*

In conclusion, I must emphasize the fact that although each method described has its distinct uses and advantages, — the McMurray probably more than any of the others, — what I said in 1940

still holds true there is no universal method of reconstruction of painful ununited femoral neck fractures, I agree with Brackett's<sup>5</sup> statement that the surgeon's choice of procedure is still paramount

520 Commonwealth Avenue

## REFERENCES

- Hermann O J Reconstructions in non ununited femoral neck fractures *Surg Gynec & Obst* 70 403-407 1940
- Colonna P C A new type of reconstruction for old ununited fractures of the neck of the femur *J Bone & Joint Surg* 17 110-112 1935

- Whitman R The operative treatment of ununited fracture at the hip *Surg Gynec & Obst* 43 221-223 1926
- Magnuson P B *Fract res* 466 pp Philadelphia J B Lippincott Company 1933 Pp 214-212
- Brackett E G Reconstruction operations for old ununited fractures of the neck of the femur *J Bone & Joint Surg* 20 93-96 1938
- McMurray J P Fracture of the neck of the femur treated by oblique osteotomy *Brit M J* 1 330-333 1938
- Cotton F J Operative treatment of hip fractures intracapsular *Am J Surg* 38 619-628 1933
- Bradford C H Personal communication
- Lorenz Cited by Campbell W C *Operative Orthopedics* 1154 pp St Louis The C. V. Mosby Company 1939 P 221
- Bossan E J A new treatment of intracapsular fractures of the neck of the femur and Calvé Legg Perthes's disease *J Bone & Joint Surg* 14 884-887 1932

## MEDICAL PROGRESS

### SURGERY OF THE AUTONOMIC NERVOUS SYSTEM

#### Method of Study, with Particular Reference to the Interpretation of Clinical Results

REGINALD H SMITHWICK, MD\*

BOSTON

TO determine the effect of autonomic nervous activity on the peripheral circulation, in both health and disease, as well as before and after operations on the sympathetic nervous system, various methods of study are available. Some involve simple tests, such as surface temperature determinations. More complicated measurements not available to all, such as those by the plethysmographic method, are frequently used. By this procedure, the number of cubic centimeters of blood passing through a unit volume of tissue per minute can be determined. Autonomic nervous impulses that are capable of modifying peripheral blood flow can be temporarily interrupted by procaine hydrochloride block. Thus, sympathetic pathways to the blood vessels of the extremities can be inactivated by the injection of the proper segments of the sympathetic trunk paravertebrally, by peripheral nerve block or by spinal anesthesia. The last, of course, applies only to the legs. Other methods of inhibiting vasoconstriction, such as heating the trunk to promote reflex vasodilation, can be used. Of particular concern are the vasoconstrictor pathways, with which man is so abundantly supplied. These are active under many everyday circumstances, as in response to cold, pain, emotion and the upright position. When activated, the sympathetic nervous system greatly reduces circulation to the extremities, as well as to the viscera, both in the presence and in the absence of vascular disease.

The state of activity of the autonomic nervous system is very dependent on environmental temperature. For this reason, controlled room temperature conditions are essential to a study of patients both before and after operation. If the patient is placed in a cool environment for a given period, with a minimum of the body surface covered, vasoconstriction is induced. The surface temperature of an extremity is then measured, or the quantity of blood flowing through a given segment is determined by the plethysmographic method. The vasoconstrictor fibers are then temporarily interrupted by one of the methods mentioned, and the surface temperature or quantitative blood flow is again estimated. One can thus tell fairly accurately how much the circulation can be increased after sympathectomy. Certain exceptions to this statement need not be discussed at this point. It is essential that the same conditions of study be used in subsequent observations.

When patients are studied in a warm environment, vasoconstriction is not induced, and may be totally absent, in fact, in higher temperature ranges, vasodilation may actually be present. Under such conditions of study, the circulation of the extremities is not primarily dependent on vasoconstrictor activity. When judged in this manner, the blood flow to the skin and subcutaneous tissues after acute denervation by procaine hydrochloride block or actual surgical excision of the sympathetic nervous system may not be significantly altered. In fact, the maximal blood flow to an extremity is somewhat decreased by sympathectomy because vasodilator, as well as vasoconstrictor, fibers are interrupted.

Reprints of articles in this series are not available for distribution but the articles will be published in book form. The current volume is *Medical Progress Annual 1940* (Springfield Ill) no 5 Charles C Thomas Company 1941 \$4.00.

\*Instructor in Surgery, Harvard Medical School assistant chief surgeon, Massachusetts General Hospital.

Thus, if one compares the surface temperature of a denervated extremity and a normally innervated extremity after exercise or after the trunk has been heated to promote reflex vasodilation in the extremities, the normally innervated extremity is the warmer. The circulation of the sympathetomized hand is nevertheless high and adequate. If, then, the patient is again observed in a cool environment, or if while he is still in a warm environment, stimuli are utilized that generally invoke vasoconstriction, such as a loud noise, immersion of an opposite extremity in cold water, or an unpleasant thought, the findings are quite different. The denervated extremity maintains its high blood-flow level, whereas the circulation of the undenervated extremity generally is greatly decreased. Operations on the sympathetic nervous system, therefore, do not increase blood flow beyond its maximal level; they stabilize blood flow near and somewhat below this point. Because the action of the autonomic nervous system in the everyday life of the average person is preponderantly in the direction of vasoconstriction, the net result of inhibiting this mechanism is an increase in blood flow to the part.

This point may be more clearly illustrated by the case of a young woman who suffered from Raynaud's disease. I had occasion to sympathetomize one of her upper extremities before she went to Europe to compete as a member of the American Olympic Ski Team. Under virtually all circumstances, the denervated hand was much the warmer. The only exception was noted after the patient had climbed to the top of the course, which required considerable physical effort. At this point, the undenervated hand was the warmer. It was also pink and moist. The denervated hand, however, was also warm and of good color, and dry. At the same time, the body was uncomfortably warm, and conditions for reflex vasodilation were present. By the time that she reached the bottom of the incline and the end of a race, however, the undenervated hand was cold and ischemic whereas the denervated hand was warm and of good color, as before the race. At this point, the body was chilled, and together with the excitement associated with the event, conditions inducing vasoconstriction were present. There was no question whatsoever in her mind concerning which hand had the better circulation day in and day out, and needless to state, the other extremity was subsequently denervated.

When, on the other hand, one is dealing with impaired circulation in the presence of known organic vascular disease, the ability of blood vessels to relax in the acutely denervated state may be already lost. In many cases, their ability to

constrict in response to nervous impulses is still preserved and can be abolished by proper surgical maneuvers. It therefore becomes increasingly imperative to stabilize blood flow at the highest possible level. That this may result in a striking increase in circulation, even in the presence of extensive obliterative vascular disease, is clear, provided one studies the patient before operation under conditions when vasoconstriction exists, and duplicates the same conditions for postoperative comparison. This seems to me to be the crux of the situation, and it is important enough to warrant a specific illustration.

Figure 1 presents the surface-temperature charts of a sixty-one-year-old man who was known to have peripheral arteriosclerosis, with obliteration of main-vessel pulsation below the femoral artery of one extremity. The other extremity also had calcified vessels, but main-vessel obliteration did not exist. Intermittent claudication of moderate severity was present in the more affected leg. After exposure of all four extremities for one hour at a room temperature of 68°F., with the patient in the horizontal position, and the body covered only by a sheet and a thin cotton blanket from axilla to groin, surface-temperature readings were taken. These were recorded at numerous points from the tip of the toe to the groin, as illustrated. The nature of the surface-temperature curves of the two extremities was similar in the undenervated state. There was no significant difference, in spite of the obvious difference in main-vessel pulsation. This type of curve, in which the surface temperatures began to fall from a high point in the extremity to the tip of a digit, indicates an unusual degree of vasospasm in response to environment. It is seen in both the presence and the absence of organic vascular disease. It is to be contrasted with surface-temperature levels in other patients with and without obvious vascular disease, in which cooling of consequence under the same conditions of study is confined chiefly to the distal portion of the foot or even to the digits only. This matter was recently discussed in greater detail.<sup>1</sup>

After exposure for one hour, the vessels of the lower extremity were acutely denervated by induction of spinal anesthesia with ensuing complete motor and sensory paralysis extending to the midthoracic level. The response of the two extremities was quite different. The surface temperatures of the extremity without main-vessel obliteration rose in a far more significant fashion, particularly in the more distal portions of the leg. On the more affected side, the surface temperature of the tip of the digit rose 5°F., and at the base, only 2°F. This was accompanied by im-

provement in color, the extremity being pink and dry by contrast with the cold, cyanotic, moist state of the tissues associated with collapsed veins and clinical signs of vasospasm, which existed in the undenervated state. These findings, together with the nature of the surface-temperature chart, indicated a worth-while result from sympathectomy.

In this case, intermittent claudication was relieved in spite of the continued absence of main-vessel pulsation. This indicates a favorable effect on the circulation to skeletal muscle, as well as the obvious increase to the skin and subcutaneous tissue. In addition, the characteristic distribution of anhidrosis involving the entire leg after

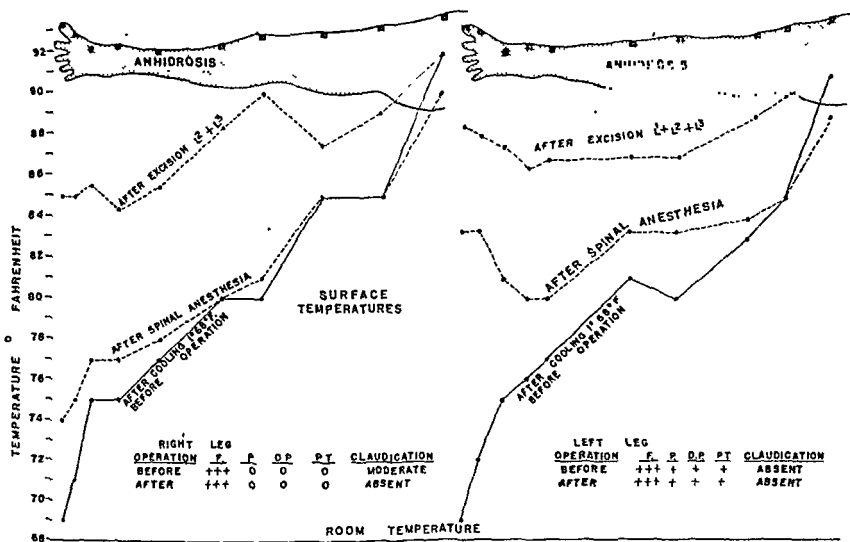


FIGURE 1.

Surface-temperature readings on both lower extremities of the same patient are compared after exposure to a room temperature of 68°F. for one hour. All four extremities were exposed, and the trunk was covered only by a sheet and thin cotton blanket from the axillas to the groin, to promote vasoconstriction. The patient was in the horizontal position. The degree of main-vessel obliteration differs in the two extremities. The effect of acute denervation following spinal anesthesia is compared with the change noted after surgical removal of certain lumbar sympathetic ganglia.

tomy in the more affected leg. There was, of course, no doubt that the circulation of the lesser involved extremity could be improved by operation, but that was not the patient's chief problem.

After operation, in response to cooling for one hour at 68°F., the surface temperatures remained much higher and were similar in the two extremities. It may therefore be stated that the circulation was significantly increased because vasoconstriction in response to prolonged cooling no longer took place. However, this does not mean that the circulation is greater in a warm environment after sympathectomy than it was before. In fact, the opposite is undoubtedly so. The one point that I should like to emphasize is that by interrupting vasoconstrictor pathways, one hopes to increase blood flow by stabilizing it somewhere near its maximal point. It should also be noted that in

excision of the first, second and third lumbar ganglia was indicated in the chart of the left leg after operation. On the right side, the removal of the second and third lumbar ganglia resulted in anhidrosis of the posterior thigh and the lower leg from the tibial tubercle distally. Figure 1 also emphasizes a clinical fact that has long been recognized: the effect of acute denervation of the blood supply to the extremities by procaine hydrochloride after exposure to and while in a cool environment does not, in the presence of the more advanced stages of obliterative vascular disease, indicate with accuracy what the effect of actual excision of appropriate portions of the autonomic nervous system will be.

This preliminary discussion of methods of study is given to present one viewpoint by which the effect of denervation of blood vessels on the

circulation of various organs and tissues of the body may be judged. I re-emphasize the fact that a quiet environment, absence of fear or worry or pain, the horizontal position and controlled room-temperature conditions are required for basal conditions of study.

#### EFFECT OF SYMPATHECTOMY FOR RAYNAUD'S SYMPTOMS

Failure to observe these fundamental rules may be the cause for differences of opinion regarding the effectiveness of sympathectomy for various disorders, and may result in erroneous deductions and conclusions. This seems to me to be part of the explanation for the conclusions reached by Johnson<sup>2</sup> in a recent article in which he finds that sympathectomy is ineffective in the treatment of patients with Raynaud's symptoms. Other reasons for the poor results that he reports will be discussed subsequently. His conclusions are based on operations performed on thirteen upper extremities and two lower extremities of 6 patients. The studies on which his conclusions are drawn are the comparison of finger volume as measured by a plethysmograph before and after operation, and at times in response to local heat, and at times in response to novocaine block of the median nerves. The conditions under which the experiments were carried out are not described. No mention is made of the position of the patient, the manner in which the body was covered or the time allowed for adjustment to whatever environment was chosen before the tests were made. The room temperature is given in three of sixteen figures and varied from 23.5 to 27.3°C., or 74.3 to 81.1°F. This clearly indicates that the conditions for study were variable and not the sort to activate peripheral vasoconstriction.

From an analysis of the figures illustrating the article in question, it is clear that the surface temperatures of the digits were high in the studies carried out before operation. They varied from 24.6 to 34.2°C., or 76.3 to 93.6°F. After operation, they tended to be slightly higher. It is therefore obvious that these patients were not studied under conditions in which the autonomic nervous system was more than partially active. Particularly I refer to Figure 14 in Johnson's<sup>2</sup> article, in which finger-volume measurements were made when the digital surface temperature was 34.2°C. (93.6°F.) before operation for comparison with the state of affairs after operation. Under such circumstances, vasoconstriction is impossible and does not exist, and sympathectomy could not and does not result in an increase in surface temperature or blood flow. The point is not that sympathectomy does not increase peripheral circulation above its maximal preoperative level. The question is,

Does sympathectomy prevent or modify a mechanism for reducing blood flow under the many conditions under which vasoconstriction exists? The answer is, In properly selected cases, the denervated extremity has a greater circulation under conditions when vasoconstriction ordinarily exists than the normally innervated extremity. This holds for normal extremities, for so-called "vasospastic disorders" and also, not infrequently, when organic vascular disease is the critical factor, such as arteriosclerosis, arteriolar disease and thromboangiitis obliterans. As organic vascular disease progresses, the maximal level of blood flow in the relaxed state decreases. The abnormal vessels, however, may still maintain their ability to constrict in response to nervous stimuli in a striking fashion. Under such circumstances, the need for modifying this latter mechanism assumes increasing urgency.

As further evidence of the ineffectiveness of sympathectomy, Johnson presents data showing that the vascular responses of an extremity to locally applied heat are not materially altered by sympathectomy. That increased blood flow to the extremity in response to local heat is controlled by local metabolic demands and not by the nervous system was shown by Freeman<sup>3,4</sup> years ago.

#### SURGICAL TECHNIC, WITH PARTICULAR REFERENCE TO DENERVATION OF UPPER EXTREMITY

It has long been recognized by many that the clinical results of postganglionic sympathectomy are not satisfactory because attacks of vasospasm recur after a few weeks, even in the absence of obvious local vascular disease, but particularly if such disease is present. Such attacks will occur in response to cold and also in a warm environment in response to emotion, such as might result from the demonstration of a patient before a group of physicians or students. The cold factor is eliminated under such circumstances. I have believed, and most observers have agreed, that this was probably the result of the action of circulating vasoconstrictor substances, and adrenin and sympathin appear to be likely ones.<sup>5-7</sup> After the preganglionic type of sympathectomy, the clinical results are far superior; such episodes as those described above in response to emotion do not occur, and vasospasm in response to cold appears only in the presence of significant degrees of local vascular disease. The attacks are milder, however, the recovery time is shorter, and the degree of exposure necessary to precipitate an attack is greater.

It is not surprising, therefore, on further perusal of Johnson's<sup>2</sup> article concerning the ineffectiveness of sympathectomy for Raynaud's symptoms, to find evidence of local fault of consequence in

some of the cases, but more particularly to find that the majority of the operations were of the postganglionic variety, which I discarded about ten years ago. In 2 cases, a preganglionic type of operation described by me<sup>8,9</sup> in 1936 and modified several times since was used. That the denervation was not complete in 1 of these cases seems possible from the response to postoperative peripheral nerve block, although as mentioned above, the surface temperature level before nerve block was so high (91°F.) as to make it impossible to draw any accurate deductions. Evidence of the presence of intact vasomotor fibers in 2 of the 3 cases in which postganglionic operations were performed is also present in Johnson's data. He prefers to ignore this, and to endow somatic nerves with a vasomotor function, to explain postoperative responses that are the result of either incomplete interruption or regeneration of the vasomotor fibers. His attempt to explain a fall in temperature in the fifth finger after median-nerve block on the basis of shunting of blood from this finger to those supplied by the median nerve is far less convincing than the suggestion that this response is due to reflex vasoconstriction in the unblocked fifth finger as a result of the discomfort or excitement attendant on the nerve block. A transient fall in temperature of the first three fingers is commonly noted during ulnar-nerve block, and of all five fingers and more proximal portions of the hand forearm and arm following paravertebral novocain block. Later, all denervated fingers reach the same high surface temperature unless the degree of local fault is more marked in some.

Atlas<sup>10</sup> has discussed the role of the second thoracic segment in the innervation of the upper extremity on the basis of a case in which this segment was not decentralized when a preganglionic type of sympathectomy was performed. He suggests that removal of the second thoracic ganglion alone is necessary to denervate the upper extremity. In this contention, he is correct. From personal observation of a number of cases in which the second thoracic ganglion was not excluded for one reason or another, it is clear that in the majority of patients, but not all, the second thoracic segment supplies fibers of consequence to the brachial plexus. However, division of the trunk above the second dorsal ganglion, with or without excision of this ganglion, excision of the second and third dorsal ganglia, and excision of the first and second dorsal ganglia have all been followed, in my experience, by significant regeneration. I have no reason to believe that simple excision of the second dorsal ganglion, which Atlas suggests as a method of denervating the upper extremity, will prevent regeneration. This major problem is recently discussed in detail.<sup>11</sup>

#### PHYSIOLOGY—BLOOD FLOW, WITH PARTICULAR REFERENCE TO HYPERTENSION

In a series of four articles, Wilkins and Eichna<sup>12-15</sup> have studied blood flow to the forearm and calf in great detail. The conditions for study were well standardized in all observations. Measurements of blood flow were made by means of a segment plethysmograph. The primary purpose of the study was to gather information concerning the peripheral circulation in cases of essential hypertension. In particular, the authors wished to determine whether the increased peripheral resistance to blood flow is due to an irreversible type of change in the walls of the arteries. Furthermore, they wished to gather more information concerning the role of the sympathetic nervous system in regulating the peripheral resistance to blood flow in both normal and hypertensive patients. In these studies, blood flow was determined in normal subjects, in patients with vasomotor disorders and in hypertensive patients. The response to various stimuli designed to activate the autonomic nervous system was observed. The effect of inactivation of the nervous system by nonoperative and operative intervention was determined. The findings are presented in detail and in such fashion that those interested in this matter will find a large number of valuable data.

These authors observe that in the forearm and calf, reflex vasodilation on warming and reflex vasoconstriction on cooling of the body are mediated by the sympathetic nervous system. It is therefore apparent that the changes in circulation in the more muscular portions of the extremities are qualitatively similar to those in the hands and feet, although they are quantitatively not so great. These reflex changes in the more muscular areas are abolished by preganglionic sympathectomy, and blood flow is stabilized at a point somewhere between the high and low levels observed in the undenervated state. As pointed out above, the blood flow in the deeper tissues is likewise reduced after preganglionic sympathectomy when compared to the maximal and increased when compared to the minimal blood flow levels observed in the undenervated state.

It is of interest that blood flow to the muscular areas of the extremities increased after sympathectomy in response to exercise exactly as it did in the undenervated state. This increase was also observed following reactive hyperemia induced by a five minute period of circulatory arrest. Moreover, blood flow to these areas increased in response to local heat after sympathectomy as before, although at the temperature level selected (40°C) the increase after operation was not quite so marked. It is therefore quite clear that certain

major physiologic responses are preserved in the denervated state, and that the necessary stimulus for their initiation is derived primarily from the tissues. A delayed vasodilator response generally induced by mental arithmetic was noted both before and after sympathectomy. This was similar to that resulting from the administration of a small amount of epinephrin. In 2 hypertensive patients, this response disappeared after adrenal denervation resulting from bilateral splanchnic and lumbar sympathectomy; it is interesting that it disappeared both in the denervated calves and in the undenervated, normally innervated arms. Muscular blood flow, which was also studied in the presence of disturbed thyroid activity, was found to vary in the same direction as the metabolic rate.

Reactive hyperemia blood flow was measured in normal and hypertensive patients. A direct relation between arterial pressure and blood flow was found in both denervated and undenervated extremities of normotensive and hypertensive patients. When the same conditions of vasodilation were imposed, there was no significant difference between the blood flow to the forearm and calf in certain normal subjects in whom rises in arterial pressure had been induced and that in certain hypertensive patients; nor was there any difference between the blood flow to the forearm and calf in certain hypertensive patients whose arterial pressures had been lowered and that in normal subjects with the same arterial pressure.

Wilkins and Eichna find their data consistent with the view that in certain hypertensive patients the blood flow to the forearm and calf during controlled vasodilation is greater than the normal for those subjects. Their study has raised doubts in their minds concerning the validity of previous conclusions that in patients with essential hypertension the vessels of the muscular segments of the limbs are involved in a generalized increased peripheral resistance that cannot be released by physiologic vasodilatation.

A series of very valuable articles and monographs has been written by Smith and his co-workers<sup>10-21</sup> in recent years concerning renal blood flow in hypertensive patients. They have devised an accurate method for measuring the quantity of blood flowing through the kidneys per minute by means of inulin and Diodrast clearances. They have demonstrated clearly that the autonomic nervous system, when activated either by pain or by emotion in the horizontal position, reduces blood flow through the kidneys by constricting the afferent arterial supply. They have also shown that renal blood flow is reduced by nervous control when the patient shifts from the

horizontal to the upright position; this is likewise due to constriction of the afferent arterioles. They also find that adrenin is capable of reducing renal blood flow but acts principally on the efferent arterioles. They observed that renal blood flow was maximal in the horizontal position, and was not increased by acute denervation of the renal blood supply resulting from spinal anesthesia. It seems reasonable, therefore, to hope that if the sympathetic nerve supply to the kidneys and adrenal glands is thoroughly interrupted by a surgical procedure, renal blood flow will be more stable and increased by comparison with the low levels resulting from vasoconstriction due to intermittent nerve impulses and reflex adrenal secretion. One would not expect it to be increased by comparison with maximal blood-flow levels in the undenervated state. Since the renal blood-flow level is almost always reduced in the hypertensive state by comparison with the normal, it is essential to stabilize and if possible to preserve what remains.

#### CLINICAL RESULTS, WITH PARTICULAR REFERENCE TO SURGICAL TREATMENT OF HYPERTENSION

Further reports of the clinical results of surgical intervention on the autonomic nervous system for essential and malignant hypertension have appeared in the literature. The operations devised vary considerably in extent. Also, the percentage distribution of cases in the different stages of the disease, as judged by eyeground changes, varies a great deal in the reported series. For example, Allen and Adson<sup>22</sup> employ an operation in which the nerve supply to the splanchnic bed is interrupted as completely as possible by an exposure that is entirely below the diaphragm. In a series of 224 patients, grouped according to eyeground changes, 5 per cent of the cases were in Group 1, 61 per cent in Group 2, 31 per cent in Group 3, and 3 per cent in Group 4. They found a significant reduction of blood pressure in 45 per cent of cases in Group 1, 35 per cent in Group 2, 26 per cent in Group 3, and 0 per cent in Group 4. For the groups as a whole, 31 per cent of the patients had a significant lowering of blood pressure.

Peet, Woods and Braden<sup>23</sup> report their experience with the supradiaphragmatic technic in which the operation is confined to the region immediately above the diaphragm. Its purpose is similar—to denervate the splanchnic bed as completely as possible by interrupting the portion of its nerve supply that is accessible at this level. The authors believed that the majority of their patients (70.7 per cent of 290 patients followed nine months to seven years) had a significant

lowering of blood pressure. Of these 290 cases, it appears that more significant evidence of lowering of blood pressure occurred in 19.3 per cent. These cases were not classified into groups according to eyeground changes. It is therefore impossible to discern the relative effect on blood pressure in the various stages of the disease. The eyeground changes were given in a series of 219 cases. In 10, the eyegrounds were normal, 13 were in Group 1, 50 in Group 2, 105 in Group 3, and 42 in Group 4. One may infer from this that the majority of the patients were in the more advanced stages of the disease.

More recently, Woods and Peet<sup>24</sup> have compared the mortality rate in 76 cases followed from five to seven years after operation with that described by Wagener and Keith<sup>25</sup> for medically treated patients. The effect on blood-pressure levels for 60 cases followed nine months or more is given. Of 4 cases in Group 1, the blood pressure was reduced in 1 (25 per cent), and of 9 cases in Group 2, a reduction occurred in 2 cases (22 per cent). Blood-pressure reduction was noted in 15 (48 per cent) of 31 cases in Group 3, and in 7 (44 per cent) of 16 cases in Group 4. The latter figures are encouraging, but the results in the cases in Groups 1 and 2 are not. Woods and Peet found the survival period in cases in Groups 1, 3 and 4 to be higher than that reported by Wagener and Keith. They noted, however, that in Group 2, the survival period was higher in the medically treated cases. The explanation for these findings is not clear. It is suggested that the significant fact was that patients in Group 2 were those with well-defined arteriolar sclerosis, without angiospasm of the retinal vessels. It is doubtful if an accurate prediction of the operative result can be made primarily on eyeground changes in the various stages of essential hypertension. Experienced ophthalmologists vary widely in their descriptions of vascular alterations in the fundi. A classification that takes into account the state of the brain, eyes, heart and kidney should be more helpful. One change about which there is no difference of opinion is the presence of papilledema. Since this constitutes the sole criterion for the diagnosis of malignant hypertension, the survival rates in Group 4 cases is significant: 33 per cent at the end of five years in the operated group, and 2 per cent in the medically treated group.

Experiences with supradiaphragmatic, subdiaphragmatic and combined lumbodorsal splanchnicectomy<sup>26</sup> were discussed by de Takats et al.,<sup>27</sup> who found the latter operation to result in a more significant lowering of blood pressure. Heuer and Glenn<sup>28</sup> report the late results of experiences with the surgical treatment of hypertension in 57 pa-

tients. Three operations were used—laminectomy, with anterior-root section, and supradiaphragmatic and subdiaphragmatic splanchnicectomy. In the opinion of the authors, the results justify a continuation of surgical attempts to relieve hypertension, but the operation should be extensive. They favor combined lumbodorsal splanchnicectomy because it is more complete than laminectomy and anterior-root section, which had to be abandoned because of the high mortality and incidence of serious complications. However, the best results, when judged by persistent lowering of blood pressure, appeared to follow this operation.

Corcoran and Page<sup>29</sup> report the effect of lumbodorsal splanchnicectomy on renal blood flow in 2 cases. There was no immediate increase; in fact, there was a decrease in both. The authors considered the effect on blood pressure to be significant, however, and suggested that in time this might result in a regression of vascular disease generally and in the kidney as well, and might, in this way, exert a favorable effect on the renal humoral mechanism.

Lumbodorsal splanchnicectomy,<sup>30</sup> which was devised more than three years ago, has been used during this period. It appears to have the advantages of both the supradiaphragmatic and subdiaphragmatic procedures, and is a little more extensive than both combined. The early results have been reported in a preliminary fashion<sup>1,30</sup> and will be given in detail this year. The operation affords excellent exposure of the kidneys and adrenal glands. Considerable information concerning the actual state of the renal blood vessels in various stages of the disease has been obtained from a study of renal biopsies. A preliminary report of these findings was made by Castleman et al.<sup>31</sup> In some cases, quantitative studies of renal blood flow have been made by Talbott.<sup>32</sup> It is hoped that these data when correlated with other detailed studies will help in the selection of cases for surgery.

Early experiences with total and nearly total sympathectomy performed in closely approximated stages in a small series of hypertensive patients were reported by Grimson.<sup>33</sup> The rationale was based on experiences with experimental hypertension in dogs. It seemed to me<sup>34</sup> that the indications for extending the surgical approach to hypertension in man beyond the splanchnic area should depend on a careful evaluation of the results of the latter maneuver and not on the results of experimental surgery. Although certain patients may benefit by greater than radical splanchnicectomy, it is doubtful if such an operation should, at present, become a routine primary procedure.



It seems quite clear that surgery has something worth while to offer the hypertensive patient. It appears that, if consistent results are to be obtained in similar cases, radical denervation of the splanchnic bed is necessary. It is also obvious that when cardiac and renal functions are both significantly impaired, operation is of no avail, however extensive. Only an occasional patient over fifty years of age is suitable for operation. When the indications for operation are clearly defined, it is to be expected that a high percentage of carefully selected patients will benefit, as judged by persistent and significant lowering of blood-pressure levels. Regression of eyeground changes, decrease in the size of the heart, improvement in the electrocardiogram, improvement of renal function and at times, of renal blood, and relief of symptoms are noted in certain cases and present additional ways of evaluating the results of surgery. Furthermore, time may show that life expectancy is increased. There can even now be no doubt of such an increase in cases of malignant hypertension and in patients with severe retinitis who have been subjected to adequate surgery before cardiac and renal functions have been seriously impaired. At the present time, surgery appears to offer the greatest hope for these patients. Perhaps, some day, a simpler solution will be attained.

319 Longwood Avenue

#### REFERENCES

- White, J. C., and Smithwick, R. H. *The Autonomic Nervous System*. Second edition. 469 pp. New York: Macmillan Co., 1941.
- Johnson, C. A. A study of the clinical manifestations and the results of treatment of twenty-two patients with Raynaud's symptoms. *Surg., Gynec. & Obst.* 72:889-907, 1941.
- Freeman, N. E. The effect of temperature on the rate of blood flow in the normal and in the sympathectomized hand. *Am. J. Physiol.* 113:384-398, 1935.
- Freeman, N. E., and Zeller, J. W. The effect of temperature on the volume flow of blood through the sympathectomized paw of the dog with observations on the oxygen content and capacity, carbon-dioxide content and pH of the arterial and venous blood. *Am. J. Physiol.* 120:475-485, 1937.
- Freeman, N. E., Smithwick, R. H., and White, J. C. Adrenal secretion in man: the reactions of the blood vessels of the human extremity, sensitized by sympathectomy to adrenalin and to adrenal secretion resulting from insulin hypoglycemia. *Am. J. Physiol.* 107:529-534, 1934.
- Smithwick, R. H., Freeman, N. E., and White, J. C. Effect of epinephrine on the sympathectomized human extremity: an additional cause of failure of operations for Raynaud's disease. *Arch. Surg.* 29:759-767, 1934.
- White, J. C., Okelberry, A. M., and Whitelaw, G. P. Vasomotor tone of the denervated artery: control of sympathectomized blood vessels by sympathomimetic hormones and its relation to the surgical treatment of patients with Raynaud's disease. *Arch. Neurol. & Psychiat.* 36:1251-1276, 1936.
- Smithwick, R. H. Modified dorsal sympathectomy for vascular spasm (Raynaud's disease) of the upper extremity. A preliminary report. *Ann. Surg.* 104:339-350, 1936.
- Idem*. The rationale and technic of sympathectomy for the relief of vascular spasm of the extremities. *New Eng. J. Med.* 222:697-713, 1940.
- Atlas, L. N. The role of the second thoracic spinal segment in the preganglionic sympathetic innervation of the human hand—surgical implications. *Ann. Surg.* 114:456-461, 1941.
- Smithwick, R. H. The problem of producing complete and lasting sympathetic denervation of the upper extremity by preganglionic section. *Ann. Surg.* 112:1085-1100, 1940.
- Wilkins, R. W., and Eichna, L. W. Blood flow to the forearm and calf. I. Vasomotor reactions: role of the sympathetic nervous system. *Bull. Johns Hopkins Hosp.* 68:425-449, 1941.
- Eichna, L. W., and Wilkins, R. W. Blood flow to the forearm and calf. II. Reactive hyperemia: factors influencing the blood flow during the vasodilatation following ischemia. *Bull. Johns Hopkins Hosp.* 68:452-476, 1941.
- Wilkins, R. W., and Eichna, L. W. Blood flow to the forearm and calf. III. The effect of changes in arterial pressure on the blood flow to limbs under controlled vasodilatation in normal and hypertensive subjects. *Bull. Johns Hopkins Hosp.* 68:477-511, 1941.
- Eichna, L. W., and Wilkins, R. W. Blood flow to the forearm and calf. IV. Thyroid activity: observations on the relation of blood flow to basal metabolic rate. *Bull. Johns Hopkins Hosp.* 68:512-521, 1941.
- Smith, H. W., Chasis, H., and Ranges, H. A. Suitability of insulin for intravenous administration to man. *Proc. Soc. Exper. Biol. & Med.* 37:726-729, 1938.
- Smith, H. W., Goldring, W., and Chasis, H. The measurement of the tubular excretory mass, effective blood flow and filtration rate in the normal human kidney. *J. Clin. Investigation* 17:263-278, 1938.
- Smith, H. W., Goldring, W., Chasis, H., and Ranges, H. A. Observations on the effective renal blood flow and functional excretory mass in man, with special reference to essential hypertension. *Am. J. Physiol.* 123:189, 1938.
- Smith, H. W., Rovenstine, E. A., Goldring, W., Chasis, H., and Ranges, H. A. The effects of spinal anesthesia on the circulation in normal, unoperated man with reference to the autonomy of the arterioles, and especially those of the renal circulation. *J. Clin. Investigation* 18:319-341, 1939.
- Smith, H. W. *The Physiology of the Kidney*. 310 pp. New York: Oxford University Press, 1937.
- Idem*. *Studies in the Physiology of the Kidney*. 106 pp. Lawrence, Kansas: University of Kansas, University Extension Division, 1939.
- Allen, E. V., and Adson, A. W. The treatment of hypertension: medical versus surgical. *Ann. Int. Med.* 14:288-307, 1940.
- Pect, M. M., Woods, W. W., and Braden, S. The surgical treatment of hypertension. Results in 350 consecutive cases treated by bilateral supradiaphragmatic splanchnicectomy and lower dorsal sympathectomy. *J. A. M. A.* 115:1875-1885, 1940.
- Woods, W. W., and Pect, M. M. The surgical treatment of hypertension: II. Comparison of mortality following operation with that of the Wagener-Keith medically treated control series: a study of seventy-six cases from five to seven years after operation. *J. A. M. A.* 117:1508-1515, 1941.
- Wagener, H. P., and Keith, N. M. Diffuse arteriolar disease with hypertension and the associated retinal lesions. *Medicine* 18:317-430, 1939.
- Smithwick, R. H. A technique for splanchnic resection for hypertension. *Surgery* 7:1-8, 1940.
- de Takats, G., Heyer, H. E., and Keeton, R. W. The surgical approach to hypertension. *J. A. M. A.* 118:501-507, 1942.
- Heuer, G. J., and Glenn, F. An evaluation of the surgical treatment of hypertension. *New York State J. Med.* 41:1922-1926, 1941.
- Corcoran, A. C., and Page, I. H. Arterial hypertension: correlation of clinical and experimental observations. *J. A. M. A.* 116:690-694, 1941.
- Smithwick, R. H. Discussion of de Takats, Heyer and Keeton.<sup>27</sup>
- Castleman, B., Smithwick, R. H., and Palmer, R. S. Renal biopsies from hypertensive patients. *Ann. J. Path.* 17:617-619, 1941.
- Talbott, J. H. Unpublished data.
- Grimson, K. S. Total thoracic and partial to total lumbar sympathectomy and celiac ganglionectomy in the treatment of hypertension. *Ann. Surg.* 114:753-775, 1941.
- Smithwick, R. H. Discussion of Grimson.<sup>23</sup>

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTE MORTEM AND POST-MORTEM RECORDS AS USED  
IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

### CASE 28151

#### PRESENTATION OF CASE

A sixty-eight-year-old physician was admitted to the hospital because of an acute illness.

Five nights before entry, the patient suddenly lost consciousness. On regaining consciousness, after about three hours, he complained of very severe frontal headache, and vomited twelve to fifteen times within the next hour and a half. In this period he felt drowsy and dizzy. Subsequently, he was kept in bed under sedation. There was occasional vomiting. Most of the time, the patient had severe headache. There were never any paralyses, pains or respiratory difficulties.

Seventeen years earlier, the patient had an appendectomy performed in the hospital, and a year later the gall bladder was removed because of chronic cholecystitis. About two and a half years before entry, he had attacks diagnosed as "coronary thrombosis" by a physician.

On admission, the patient appeared drowsy, but co-operative and well oriented, complaining of severe frontal and temporal headache. The face was plethoric, and the pupils reacted hardly at all to light. The right fundus showed blurring of the disk and distention of the veins. The neck was moderately stiff. There was a Babinski plantar response on the right, and a questionable Babinski response on the left. There were no other abnormal reflexes, and no muscular weaknesses or sensory changes. The heart was enlarged to the left, and a harsh, rough, apical systolic murmur was audible all over the precordium.

The temperature was 98.6°F, the pulse 50, and the respirations 10. The blood pressure was 140 systolic, 65 diastolic.

The Hinton blood reaction was negative. The urine showed a + test for albumin, with occasional red and white and epithelial cells in the sediment.

An electrocardiogram showed sinoauricular tachycardia (rate 145 to 150), slurred QRS complexes, diphasic T<sub>1</sub> and T<sub>2</sub> waves, moderate left-axis deviation and a rare ventricular premature beat.

On the second hospital day, after returning to bed from the toilet, the patient suddenly cried out because of pain in his head, and lost consciousness.

There were no convulsive movements, or marked changes in color. About ten minutes later, Cheyne-Stokes respirations appeared. The patient's face turned gray, and the lips flaming red. The neck was somewhat resistant to bending forward. The right eye turned outward, and the left was fixed centrally. The heart was regular, except for slight variation with respirations (pulse 60 to 70). There was no change in the heart murmur. The lungs were clear. Suddenly, the patient became very flushed, with gasping respirations and coarse tracheal rales. The patient soon stopped breathing, cyanosis deepened, and the heart beats ceased.

#### DIFFERENTIAL DIAGNOSIS

DR MAURICE FREMONT-SMITH. There are three hurdles in this case that I may not be able to clear. In the first place, we do not have any past history, except some noncontributory data such as appendectomy and cholecystectomy, which had nothing to do with the present situation. We do know that the patient was sixty-eight years of age, was said to have had a coronary thrombosis and was, according to the history, running along well until he had this sudden difficulty.

The second hurdle is that we have no record of a lumbar puncture and examination of the spinal fluid. I assume that if a case has had a spinal-fluid examination it is a neurologic case and a neurologist discusses it, if it does not, it is a medical case and a medical man discusses it.

The third hurdle, the chief one, is the limitation of a medical man in the discussion of things neurologic.

Five days before he came in, the patient had a sudden acute episode that could be interpreted only as an intracranial accident, with the rapid development of increased intracranial pressure. He became unconscious and vomited frequently. He had severe headache. The onset was extremely sudden and, in a man of sixty-eight, suggests some sort of vascular accident; the stiffness of the neck makes one believe that subarachnoid hemorrhage was the likeliest diagnosis. On the other hand, it is unusual to have subarachnoid hemorrhage at this age. It is usually the result of congenital anomaly, and usually occurs earlier than this. Moreover, with a subarachnoid hemorrhage as with any type of meningeal irritation, fever is the rule, and this man had no fever. I remember, in discussing a case a few weeks ago, Dr Kubik brought up the fact that, with subarachnoid hemorrhage, very frequently albumin and red cells of unknown origin appear in the urine, so that we can accept the albumin in our hypothetical diagnosis of subarachnoid hemorrhage. On the other hand, further possibilities must be considered. Was

this man well, or was he having some symptoms before the onset of this acute episode? He could have had a brain tumor, and this sudden episode could have been hemorrhage into the tumor. If so, we must assume that the hemorrhage had extended into the subarachnoid space, because he had meningeal irritation. He could have had meningitis, but a meningitis is usually much slower in onset and there should be some fever. Unconsciousness would come late. Lumbar puncture would be almost essential in making this diagnosis.

The patient could have had some sort of injury. He might have fractured his skull previously; we have no history. He might have had a subdural hematoma. There again, the blood must have gone into the subarachnoid space. He might have had a subacute bacterial endocarditis with embolism to his brain. He was very old for that, but he had a rough systolic murmur. I should like some comment from the neurologist afterward. I believe it would be very unlikely to have meningeal signs from such a lesion. We have the interesting fact that the patient had no paralysis. He had a Babinski response on the right, and a questionable one on the left. So that if we try to localize it, we should assume the greater injury or difficulty on the left side of the cerebrum. On the other hand, when the choked disk was described, it was the right fundus that showed blurring, and I am unable to interpret the development of this unilateral choked disk. I believe that it must be very important. It is a very rapid development: within five days, the patient had a markedly choked disk on one side. I do not know how to explain that.

Regarding embolism from the heart, if the patient had had an old coronary thrombosis he might have had a thrombus in the left side of the heart,—a mural thrombus,—and he might have thrown that off into the brain. On the other hand, the electrocardiogram does not suggest coronary thrombosis. I should interpret the electrocardiogram as showing arteriosclerotic coronary heart disease, but without evidence of thrombosis.

It is interesting that he was allowed out of bed in the hospital after this accident. Either it was against orders or they did not think he was seriously ill. He got out of bed, walked to the toilet, had a recurrence of whatever happened to him originally, and died with increasing signs of intracranial pressure and some localized paralysis of the right eye or both eyes. I am going to ask subsequently if the neurologist will make a comment about this. I cannot understand the lesion behind that type of paralysis.

Accordingly, because he was sixty-eight years old, I believe the patient had a vascular accident of some type, perhaps a subarachnoid hemorrhage. He had a low blood pressure. Did he always have it? Was the blood pressure usually high, and did it come down either because of cardiac insufficiency or because of the shock occasioned by his recent lesion? If he had had increasing or increased intracranial pressure, the blood pressure should have risen. The blood pressure, however, was not high, but the pulse was slow; he had choked disks, and he had, I think, increased intracranial pressure. I should like to leave the case open for discussion from the floor and ask the neurologic experts to add something.

My diagnosis is intracranial vascular accident, probably subarachnoid hemorrhage. If the patient had had an intraventricular hemorrhage, I think he would have been sicker, have had convulsions, and not have regained consciousness; and I think it is more likely a straight subarachnoid hemorrhage. Without hypertension, I suppose that, even at this age, the basis for hemorrhage was a congenital aneurysm.

DR. WILLIAM B. BREED: I am not a neurologist, but I should like to ask a question. Do you think perhaps the meningeal, subarachnoid phase of this has been overemphasized? The only evidence is some stiffness of the neck, only slightly painful.

DR. FREMONT-SMITH: It is quite important evidence. One sees a patient with almost no neurologic signs, perhaps a headache, but if only slight stiffness of the neck is present one may suspect a diagnosis of encephalitis as against a simple upper respiratory infection. I think that this sign is important if present. One thing to remember is that in stiffness from meningeal irritation the neck resists forward bending, but the head can be easily turned from side to side. In arthritis, on the other hand, all motions of the head are painful. I prefer to believe that the symptom is important in this case.

A PHYSICIAN: Does it not say later that it became stiff?

DR. FREMONT-SMITH: The last note says, "The neck was somewhat resistant to bending forward." I should accept that as an important sign.

DR. TRACY B. MALLORY: Does anyone care to comment on Dr. Fremont-Smith's question regarding meningeal irritation secondary to emboli from a bacterial endocarditis?

DR. CHARLES S. KUBIK: We have had a fair number of cases in which cells, although usually no organisms, were present in the spinal fluid and a subarachnoid exudate was found on post-mortem examination. The condition presumably results

from emboli to meningeal vessels. Another possibility is bleeding from a mycotic aneurysm.

In answer to Dr. Breed's question, another point in the history must be considered. All this patient had was a stiff neck and headache, but the symptoms came on suddenly, and at the onset he lost consciousness.

DR JAMES B AYER: I saw this patient at home on the third day of his illness. He was mentally clear, admitting slight headache. Except for slight stiffness of the neck, neurologic examination was negative. The heart was as described. I believed that we were dealing with cerebral embolus and asked Dr. Paul White, who had followed him, if the heart was consistent with this diagnosis. He agreed. I saw the patient the next day. The neck was still very slightly stiff, and there was still headache. Kernig's sign was absent, and the fundi were normal. Although the diagnosis of cerebral embolus still seemed to me correct, it was decided to send the patient to the hospital for further study. A lumbar puncture was planned for the morning of his death. Had it been done before death, I should certainly have considered it a contributing factor. As it was, his unexpected walk to the toilet room seems to have been the predisposing act. The second episode naturally weakened my opinion about the diagnosis of embolus. Yet we had no evidence for tumor or any long standing disease other than that of the heart. I was reticent about making a diagnosis of spontaneous subarachnoid hemorrhage, and still favored the diagnosis of embolus.

A PHYSICIAN: I wonder if you would say a word about the ocular paresis.

DR. AYER: Yes; there was a slight paresis, which certainly was a little in favor of Dr. Fremont-Smith's diagnosis.

DR. JACOB LERMAN: Did Dr. Fremont-Smith commit himself about the heart?

DR. FREMONT-SMITH: I did say that I thought the electrocardiogram gave no evidence of prior coronary thrombosis.

#### CLINICAL DIAGNOSES

- Cerebral hemorrhage?
- Cerebral embolus?
- Old myocardial infarction.

#### DR. FREMONT-SMITH'S DIAGNOSIS

Subarachnoid hemorrhage from congenital aneurysm.

#### ANATOMICAL DIAGNOSES

Congenital aneurysm of right internal carotid artery and circle of Willis, with rupture and hemorrhage into subdural and subarachnoid space.

Cardiac hypertrophy, hypertensive type.

Infarct of heart, healed.

Arteriosclerosis, marked, generalized.

Nephrosclerosis, moderate.

Operative scars. cholecystectomy and appendectomy.

#### PATHOLOGICAL DISCUSSION

DR. MALLORY: The heart was hypertrophied and showed marked diffuse coronary sclerosis. All the vessels were narrowed down to pinpoint lumens, but there were no points of complete occlusion. The left ventricle showed considerable patchy fibrous scarring of the inner third of the myocardium, consistent with old infarction, two or three years old perhaps. There was no overlying thrombus, however, and no thrombi in any of the other cavities, and there were no valvular deformities or anything to explain the heart murmur.

DR. KUBIK will describe the cerebral findings.

DR. FREMONT-SMITH: May I ask Dr. Bland if it is usual for an old coronary thrombosis to give a later electrocardiogram like this?

DR. EDWARD F. BLAND: It may be anything from normal to the findings recorded here.

DR. MALLORY, would you be willing to comment on emboli following coronary thrombosis? It often comes up in these discussions.

DR. MALLORY: It is my impression that, if an embolus occurs following infarction, it follows after a relatively brief period; in the first month, it is not unusual, but subsequent to that it is quite uncommon.

It is generally true that emboli from a mural thrombus overlying an infarct are apt to be large massive ones, not the type that might plug a small vessel in the brain. It is more apt to be an enormous embolus that goes down the aorta and forms a rider at the bifurcation of the iliac arteries or plugs the whole femoral artery on one side.

DR. KUBIK: There was a ruptured aneurysm in the outer angle between the right internal carotid and posterior communicating arteries. Although these are called congenital aneurysms, it is quite possible that they may not always date from birth. They always occur in the fork between a larger artery and one of its branches, or between two branches of the same size. It is not uncommon to find a defect in the media at this point. It is the defect that is congenital, and an aneurysm is probably an enlarged defect, which, in some cases, is present at birth but may develop, in other cases, after birth on the basis of the congenital defect. There is no media in the wall of the aneurysm, only intima and adventitia. Most of those observed in this laboratory have involved the internal

carotid, middle cerebral or anterior cerebral artery. There have, I believe, been only two of the basilar artery.

DR. MALLORY: I think it is fair to say that as we have become increasingly conscious of the relation of aneurysms of this type to cerebral accident, and particularly to subarachnoid hemorrhage, we are finding them with considerably increased frequency even in people beyond fifty, as in this case.

A PHYSICIAN: May I ask about the kidneys?

DR. MALLORY: They showed very slight contraction consistent with a slight degree of hypertension. The patient may very possibly have had hypertension before his cardiac infarct. I do not know specifically.

DR. HENRY R. VIETS: Was there much blood in the subarachnoid space, or little?

DR. KUBIK: There was a good deal.

DR. VIETS: It is interesting that he did not have convulsions.

DR. KUBIK: The hemorrhage had not extended into the substance of the brain, as it sometimes does.

DR. VIETS: We can say, then, that the stiff neck was important.

DR. ALLEN G. BRAILEY: Was not the low blood pressure an unusual finding?

DR. MALLORY: The patient may well have had a hypertension that disappeared with the cardiac infarct. That is not an uncommon story.

## CASE 28152

### PRESENTATION OF CASE

A twenty-seven-year-old housewife was admitted from an outside hospital, because of coma, following stiffness of the neck.

A week before entry, the patient awoke one morning with a stiff neck. There were no other complaints. A physician found the neck to be fairly rigid, with some voluntary spasm of the right trapezius muscle. The neck could be moved laterally without much difficulty, and could be flexed passively. The blood pressure was 145 systolic, 90 diastolic, seated. The temperature, pulse and respirations were normal.

There was no history of antecedent trauma. Ten years previously, the patient had been operated on for a benign ovarian cyst.

The neck was treated with local heat and rest. In the next three days, there was much improvement, so that the patient went to a dance, feeling well. The next afternoon, the stiffness in the neck returned, and local heat failed to help. Two days before entry, the patient again consulted her phy-

sician. Examination showed inability to flex the head because of pain and stiffness on the right side of the neck, extending upward to the right occipital region. Lateral motion was restricted on the left, but fairly free on the right. The reflexes were normal, with a negative Kernig's sign. The pupillary reactions and the fundi were normal. The temperature, pulse and respirations were normal. Bed rest, aspirin and local heat were advised. On the morning of entry, the patient complained of headache centering in the right parieto-occipital area. A cough made her feel "as if the top of the head were coming off." The pupils were small, and reacted poorly to light. She was admitted to an outside hospital, with a temperature of 98.8°F., a pulse of 68 and respirations of 20; the blood pressure was 150 systolic, 90 diastolic. Examination of the blood showed a white-cell count of 12,000. The urine was normal. The patient was put to bed, and given sedation. She dozed for an hour, then awakened suddenly and cried out in pain. The right arm and leg twitched. She was unable to speak, but seemed oriented. The pulse was 60, the respirations were shallow, and there was slight cyanosis. Oxygen and intramuscular magnesium sulfate and caffeine were given. In about three minutes, there was gradual recovery. The blood pressure was then found to be 210 systolic, 110 diastolic. The patient was fully conscious, rational and able to talk. She said that her headache had abated. She remained quiet for about two hours, when there was a second attack similar to the first. The right arm and leg twitched, and then became fixed in rigid extension, with the right foot in Babinski position. After twenty minutes, the left arm and leg progressed through a similar phase of twitching to a similar type of spasticity. The rigidity of the neck had disappeared. There were no facial twitchings. The pupils were constricted. There was continued unconsciousness. The systolic blood pressure varied between 160 and 180. The respirations were shallow, varying from 20 to 30, and even in an oxygen tent the color was dusky. The pulse remained at 60. The patient was transferred to this hospital by ambulance.

On admission, the patient was apneic, with a pulse between 130 and 150. There was some question of early edema of the medial sides of both optic disks. The patient was maintained in a respirator for about an hour, when the heart stopped.

### DIFFERENTIAL DIAGNOSIS

DR. CHARLES S. KUBIK: A young woman was admitted in coma, following stiffness of the neck of a week's duration. There was no paralysis.

If, as one may assume, the patient had been in good health, there are not many diseases that would result in such a sequence of events. One might think of meningitis and spontaneous subarachnoid hemorrhage, but meningitis ought to be ruled out by the absence of fever and by a temporary remission of symptoms. There is still another reason for ruling out meningitis. This patient did not have any headache until several days after the onset of her illness. The absence of headache, to be sure, very nearly rules out subarachnoid hemorrhage. Headache is usually the first and one of the most prominent symptoms, but there are occasional cases without headache. I have heard of two, and there is a patient in the hospital now whose headache, which was severe at the onset, quickly subsided although the neck was rigid and movements of the neck were painful, the pressure was very high, and there were signs of active bleeding in the form of convulsive seizures and increasing hemiparesis.

But, returning to the case under discussion, one week or so after the onset of stiffness of the neck the patient did complain of headache, centering in the right parieto-occipital region, and when she coughed it felt as if the top of her head were coming off. These symptoms were more typical of hemorrhage and increasing intracranial pressure. Then, shortly after being admitted to the outside hospital, she cried out with pain, which, I assume, signified a sudden increase in the severity of the headache; however, it may have been due to pain in the neck, or both. In any event, the sudden onset and severity of this pain compel one to think of bleeding, and nothing else.

From this point on, the course was more or less characteristic of severe intracranial hemorrhage, and consistent with subarachnoid hemorrhage that had broken through the pia mater into the brain or ventricle, with a marked and rapid increase in intracranial pressure. Such a situation best explains the seizures, elevation of blood pressure, slowing of the pulse, shallow respirations and, finally, respiratory failure. Toward the end, the pulse became rapid, presumably because of paralysis of the vagal centers in the medulla.

Could this have been a cerebral or pontine hemorrhage? I should think not. The patient was young; she did not have hypertension or, at any rate, not marked hypertension, and there was no paralysis.

I recall a case of cerebellar hemorrhage, with rupture into the fourth ventricle, that ran a course similar to that of subarachnoid hemorrhage. In that case, I believe, there was considerable vertigo. I mention this because of the right sided pain in the neck but have no right to offer it as a diagnosis.

The possibility of cerebral or cerebellar tumor, other than vascular tumor and of abscess or subdural hematoma can, I should think, be dismissed without any further comment.

If this was a subarachnoid hemorrhage, what and where was the source of the bleeding? By far the most common cause, as you all know, is so called "congenital aneurysm." Less common causes are varices, cavernous hemangioma, hemangioma of choroid plexus, mycotic aneurysm and hemorrhagic disease. I do not see any special reason for suspecting any of these less common conditions, and my diagnosis will therefore have to be ruptured congenital aneurysm. The violence of the terminal stage of the illness suggests arterial rather than venous bleeding.

The aneurysms, in my experience, are most often found on the internal carotid, middle cerebral or anterior cerebral arteries, occasionally on the basilar. In this case, possible leads to localization are somewhat bewildering. Rigidity of any pain in the neck, without headache, observed at the onset, might point to the posterior fossa. A small amount of bleeding there might conceivably cause considerable rigidity of the neck without increasing intracranial pressure very much. Small pupils, reacting poorly to light, also suggest a disturbance in that locality. It is a matter of experience that fixed pupils in subarachnoid hemorrhage are of no localizing value, but the pupils in this case also became constricted, and that might mean something. There were no other signs of cranial nerve involvement to help one in making a localization.

What can one do with the seizures? These began on the wrong side,—that is, on the same side as the headache,—then involved the other side, and were followed by what was probably extensor rigidity. They might suggest aneurysm of the internal carotid, middle cerebral or anterior cerebral artery, possibly the anterior cerebral, which lies in the intercerebral fissure, so that the hemorrhage might have extended first into one and then into the other frontal lobe or, what is commoner, upward through the rostrum of the corpus callosum into the anterior horns of the lateral ventricles. But if that had been the site of the bleeding, one would have expected frontal headache and pain back of the eyes. I believe that I have seen seizures such as these, and extensor rigidity as a terminal event in subarachnoid hemorrhage even when there was not extensive hemorrhage into the substance of the brain. The ventricles may even be distended with blood entering through the cistern, fourth ventricle and aqueduct. Perhaps the seizures are not of localizing significance and can be explained by an aneurysm of the basilar artery rupturing into the third ventricle. I have

that takes cognizance of the adroit and intelligent manner in which he has handled the promotion of the Society's medical-service plan in Massachusetts.

## NATIONAL FOUNDATION FOR INFANTILE PARALYSIS

THE National Foundation for Infantile Paralysis has completed three years of work since its organization. This new and active group, covering the entire field of investigation into the cause, prevention and amelioration of poliomyelitis, is supported by a fund-raising agency, the Committee for the Celebration of the President's Birthday. Through various medical committees, activities are carried out in virus and nutritional research, the prevention of aftereffects, the study of epidemics and the dissemination of educational information.

In 1941, according to the annual report,\* the largest grants for research went to the virus-research committee. A sum of over \$185,000 enabled investigators in many states to pursue their studies. Large grants were made to the School of Public Health of the University of Michigan, the George Williams Hooper Foundation of the University of California, Yale University School of Medicine, the United States Public Health Service and others. The University of Wisconsin received over \$60,000 under the committee on nutritional research. The work on aftereffects, carried on in many laboratories and hospitals, was made possible by grants totaling over \$150,000, and the fields of epidemics and education were not neglected. Thus, a total of over \$800,000 was used to combat poliomyelitis in 1941.

It is naturally impossible at this time to evaluate the results of the expenditure of such a large sum of money on the study of a single disease, particularly since many of the grants were for the continuation of studies that will not end for some years to come. One may say, however, that the work of the National Foundation for Infantile Paralysis in three years has profoundly affected present-day knowledge of the disease by making

a broad and continuous attack on many fronts. New light has been thrown on the widespread nature of poliomyelitis, the problem of the healthy carrier, transmission of the disease by flies, the retention of the virus in sewage, the entrance of the virus into the body by various routes, the use of animals other than the monkeys for experimental purposes and new means of virus identification. In the field of aftereffects, the sponsoring of the investigations of Miss Elizabeth Kenny's technic of treatment has been outstanding. In view of previous criticism of this method, the decision of the foundation to investigate was not reached without long deliberation; however, the subsequent endorsement of the Kenny treatment by the Medical Advisory Committee is proof of the value of the foundation's farsighted policies. The educational needs have been met by grants for schools of nursing, scholarships, conferences and publications. Many field studies have been carried out by the Committee on Epidemics and Public Health. In general, material advances have been made, investigation has been stimulated and new knowledge has been added to the subject of poliomyelitis by the work of the foundation.

## MEDICAL EPONYM

### NÉLATON'S LINE

Professor Auguste Nélaton (1807-1873), surgeon of the Saint-Antoine Hospital, of Paris, called attention to this line in his *Éléments de Pathologie Chirurgicale* [*Elements of Surgical Pathology*] (Paris: Germér Baillière. 2: 441, 1847). A portion of the translation follows:

If the exact relations of the great trochanter to the various bony prominences of the pelvis be examined in their normal state, it will be found that when the femur is flexed to a right angle and slightly adducted, the top of the great trochanter falls in a line that extends from the anterior superior spine of the ilium to the most prominent portion of the tuberosity of the ischium, and that this line divides the cotyloid cavity into two equal parts. This line, corresponding to the center of the cotyloid cavity . . . may easily serve as a guide to measure the degree of displacement [of the head of the femur]. . . . For this purpose, it suffices, after the thigh has been flexed to a right angle, to place a tape on the two points indicated,— that is, the anterior superior spine of the ilium and the ischial protuberance,— and to explore the gluteal region of both the sound and the injured side, to observe the difference between the two.

R. W. B.

\*The National Foundation for Infantile Paralysis, Incorporated: Annual report, 1941. Publication No. 38 of the Foundation. 58 pp. New York: National Foundation for Infantile Paralysis, Incorporated, 1941.

## MASSACHUSETTS MEDICAL SOCIETY

## TREASURER'S REPORT

## COVERING REFUND DISTRIBUTION

The treasurer of the Massachusetts Medical Society makes the following report regarding the refund to district societies for 1942:

The Council voted to distribute the sum of \$4000 to district societies. The total number of payments of annual dues received by the treasurer by March 4, to be counted for the refund, was 4023. Therefore the refund to the district societies for each paid fellow is \$0.994.

The following table gives the number of payments as of March 1, and the refund to each district as of March 31:

DISTRICT	NUMBER REPORTED PAID	REFUND
Barnstable .....	41	\$40.75
Berkshire .....	108	107.35
Bristol North .....	58	57.65
Bristol South .....	163	162.05
Essex North .....	180	178.95
Essex South .....	233	231.60
Franklin .....	36	35.82
Hampden .....	293	291.25
Hampshire .....	52	51.70
Middlesex East .....	123	122.26
Middlesex North .....	109	108.35
Middlesex South .....	779	774.33
Norfolk .....	697	693.82
Norfolk South .....	122	121.30
Plymouth .....	116	115.30
Suffolk .....	492	489.05
Worcester .....	346	343.92
Worcester North .....	75	74.55
Totals .....	4023	\$4000.00

In 1941, for comparison, the total number of payments for the refund was 4038.

CHARLES S. BUTLER, M.D., *Treasurer.*

## COMMITTEE ON MATERNAL WELFARE

CASE HISTORY: RETAINED PLACENTA FOLLOWED  
BY UTERINE AND TUBAL ABSCESSES AND DEATH

A seventeen-year-old primipara had had adequate care from the fourth month of pregnancy. Physical examination was negative, and the past history was irrelevant. Labor was complicated by a breech presentation, the labor itself being normal. The breech was delivered without difficulty. The baby weighed 6 pounds, lived only an hour, and showed numerous deformities, among them clubfeet, spina bifida and hydrocephalus.

The placenta separated in part immediately because there was considerable hemorrhage, but it did not come away spontaneously. An hour after delivery, the patient was in shock. The placenta had not been obtained, and attempts to remove it were abandoned. During the night following delivery, there was more bleeding, the blood pressure falling to 80 systolic, 75 diastolic, with a pulse of 140. On the following morning, some fragments of placenta were obtained with a placental curette. A few hours later, the placenta was expelled spontaneously. Fifteen minutes after this, the patient had a chill, the temperature rising to 106°F. A high fever persisted until death, which occurred twenty-seven days later. The patient during this septic course was transfused twice and was given sulfanilamide. Autopsy showed an abscess of the right cornu of the uterus and of the right fallopian tube, with metastatic abscesses in both lungs.

*Comment.* This infection was probably due to attempts to remove the retained placenta, which may have been slightly adherent but was certainly not an accreta, as proved by autopsy. Autopsy also showed that the infection started in the uterus and became a blood-stream infection, with localized abscesses in the lungs. The sulfanilamide therapy was probably unintelligent. There was no evidence of uterine or blood culture on which to base this chemotherapy, but the patient was treated at the beginning of the era of chemotherapy, before proper standards had been established.

Retained placentas are inherently serious complications. So long as an adherent placenta or a retained placenta is unaccompanied by hemorrhage, it is wisest to leave it alone, often for as long as twenty-four hours—in the absence of bleeding—before manual attempts to remove it. Frequently, before the end of twenty-four hours, the placenta separates itself and is delivered spontaneously. In the presence of actual bleeding, the uterus must be invaded under the strictest asepsis. In no other way may a diagnosis be made and hemorrhage controlled. A retained placenta is easily removed, and a lightly adherent placenta may be manually separated from the uterine wall and removed intact. A placenta accreta can be diagnosed only by intrauterine examination. An accreta so diagnosed demands hysterectomy.

It is always wise to pack the uterus from which an adherent placenta has been manually removed. This is done for two reasons: to guard against subsequent hemorrhage; and to hasten the separation of small areas of placenta that have not been removed.



## "THE CARE OF CRIPPLED CHILDREN"\*

The Massachusetts Department of Public Health has recently completed its first five years of Services for Crippled Children. These services were made possible by a federal grant-in-aid authorized by the Social Security Act of 1935.

During this period, more than 2000 children who probably would not otherwise have been able to receive medical and surgical care and aftercare were admitted to the ten state-wide clinics that minister to crippled children. This service has cost a little over \$400,000, including hospital care, so that the average expenditure for each child has been less than \$200.

More than 600 of the 2000 crippled children who came to the clinics needed immediate surgical help, and were at once admitted to hospitals for operation. More than 150 had to have more than one operation. One had to be admitted to a hospital six times, and another child remained in the hospital continuously for twenty months.

These crippled children came largely from rural regions where there are few opportunities for them to receive the care they need. Even so, it is a matter of surprise that so many neglected crippled children actually were found because, as compared with other states, the Commonwealth is unusually well supplied with both public and private agencies that have for years been engaged in the humanitarian work of aiding the handicapped child. In administering this program, the department has been very careful to avoid supplanting the work of any of these agencies. The purpose of Services for Crippled Children has been solely, in the words of the Social Security Act, "to improve and extend existing services."

As a result of a study of what has been accomplished for crippled children by the Department of Public Health during the last five years, several interesting things have been learned.

### AGE AND SEX OF CRIPPLED CHILDREN

More children come to clinic for the first time when they are in their sixteenth year than at any other age. If these adolescents came for help because of deformities caused by accidents or infections, one might conclude that they had been injured in their early teens, when children are on the streets more than when they are younger. But this is not so, for the great majority of patients at this age have had their disabilities for years.

The reason for not seeking aid sooner can only be inferred. That the age of sixteen is the most popular one at which to go to a clinic for help is particularly true of boys. Girls report in gradually increasing numbers beginning at the age of thirteen, through fourteen, fifteen and sixteen. One must conclude that many of the patients at the adolescent age, both boys and girls, come on their own initiative when they begin to take an interest in themselves and in their appearance. This change begins at a younger age in girls than in boys, and reaches its climax at sixteen in both boys and girls.

More than a third of all crippled children admitted to clinics came because of crippling conditions that they had had ever since birth. Most of these children were not seen until they were ten to fourteen years of age. However, the Department of Public Health has been offering this service for five years only, and many children had no opportunity to get aid earlier in life. Now that the clinics

are more widely known and have achieved considerable reputation for excellent care, such children will probably apply for treatment at younger ages.

The reasons why parents do not bring their children to clinics at younger ages are several. They realize that treatment and apparatus are expensive, they fear the surgical operations that are so often necessary, and they think that the crippling condition is so hopeless that nothing can possibly be done to alleviate it. There are also, of course, those who believe that a deformity has been bestowed by the Deity and, therefore, should not be disturbed. On the other hand, certain parents will not regard a deformity as hopeless, no matter who has told them so, and go to every clinic and to every physician who can speak with authority, in the vain hope of finding someone who will promise physical restoration.

### PROCEDURE FOR ADMISSION TO CLINICS

To be admitted to a clinic, a crippled child need only present an application signed by a physician licensed to practice medicine in the Commonwealth, preferably the family physician. A child thus admitted is given a thorough examination at the clinic, following which a complete social study of the patient's family is made by a public-health social worker. If this social study indicates that the child would be unable to obtain all the medical and surgical attention he needs without state or charitable aid, he is accepted for care. The information obtained by the social worker is also referred to the chairman of a special committee of the district medical society for an expression of his opinion concerning the child's eligibility for public care. Every effort is made to exclude from clinics all persons who are able to pay and who should pay for all the necessary treatment and apparatus. The final decision of eligibility for admission to a clinic rests with the Commissioner of Public Health. If patients can afford part of the services rendered, arrangements are made for them to pay the hospital or the brace maker.

### PHYSICAL THERAPY

Many of the patients seen at the clinics do not require operations; they may need no other treatment than physical therapy. In such cases, the clinic consultant prescribes the treatment he wishes given, and arrangements are made for the physical therapist of that clinic district to visit the home periodically to carry out these recommendations. Where there are several patients in a community who require such treatment, they are brought together, if possible, at some convenient center and are there given treatment; the time of the physical therapist is thus conserved. Such an arrangement is not often possible, for most of the patients live in rural regions at some distance from each other. To have such patients brought to a central point would require transportation and the time of some other member of the family. The mother would generally not be able to take the time to go with the child, and thus one of the most important functions of the physical therapist would be lost—that of teaching the mother or an older sister what treatment to give and how to give it.

### PREVIOUS MEDICAL AND SURGICAL CARE

Over 500 children had never had any medical or surgical treatment when they first came to a crippled children's clinic. That such a situation existed in the Commonwealth has surprised those who insisted, before the Orthopedic Unit was organized, that few neglected children would be found. In all justice to the medical

\*A "Green Lights to Health" broadcast given through Station WAAB by Dr. Edward G. Huber on Saturday, January 31, and sponsored by the Public Education Committee of the Massachusetts Medical Society and the Massachusetts Department of Public Health.

profession, it must be said that the reason for the neglect of these children was not that physicians had refused to help them but that the parents had made no effort to obtain care for their children. The tendency in some families is to hide the deformed child from other than members of the family, and thus to become so accustomed to the sight of the crippling condition that all thought of making the necessary efforts to correct the condition disappears.

Several hundred crippled children had had no other help before coming to the state clinic than the advice of their family physicians. It must be remembered that these children are a rural-dwelling group and that under such conditions the family physician's help is largely limited to giving advice, since he cannot afford to provide hospitalization or apparatus. The only hospitals ordinarily available to rural patients are the smaller ones where free beds are not numerous and clinics are few. The Orthopedic Unit makes a particular effort to extend Services for Crippled Children to just such areas, to find and care for these children.

Over 300 of the clinic patients had had previous treatment in some metropolitan or local hospital. Practically all these children had had operative treatment, and this had nearly always been well done. But no matter how successful an operation, unless there is efficient aftercare and follow up, much of the beneficial effect is lost. This was true in many of the patients seen in the clinics who had had operative procedures some years before admission, but who had had no aftercare. Many of them needed another operation, which might not have been necessary if they could have had good aftercare.

Many parents brought their children to the state clinic because they had found it necessary to discontinue the treatment their children were receiving, because of lack of sufficient funds. Treatment for crippled children generally extends over several years and expensive apparatus is frequently necessary.

More than 100 others discontinued their previous treatment because they had reached the age limit established by the agency under whose care they had been. Since patients are accepted at the clinic centers up to the age of twenty-one years, this is an excellent way to fulfill one of the purposes of Services for Crippled Children—to extend existing services.

#### ACCEPTANCE OF RECOMMENDATIONS

The recommendations of clinic consultants are surprisingly well accepted. No special efforts are ever made to induce anyone to consent to operation. The risks and the possibility of unsatisfactory results, as well as the possible benefits to be derived from surgical interference, are explained to each patient's family. On the other hand, a parent's first refusal is rarely accepted as final, especially if there are good chances for improvement in that child's condition. The unco-operative patients are discharged from a clinic only after they finally and definitely refuse to accept aid, and after the clinic consultant and several members of the field staff have repeatedly talked with them.

Any patient who has been dropped from the active list because of refusal to accept the aid that has been offered may, of course, be readmitted at any time that the parent changes his mind and decides to accept aid. Occasionally, in flagrant cases of neglect, the Society for the Prevention of Cruelty to Children is called on for aid, which is gladly given. A child should not be penalized for life because ignorant parents refuse to allow him to have his handicaps overcome.

It is remarkable that only a few have refused aid. This is a tribute to the clinic consultants and to the field workers, physiotherapists and social workers alike, who interpret the orthopedists' recommendations to the families. Most of the refusals came early in the program, they are rare now that the clinics have achieved a well-earned reputation for obtaining satisfactory results.

One cogent reason for this reputation lies in the continuity of the service offered, once the patients are accepted. They are examined by the clinic consultant, who is aided by the clinic supervisor, the physical therapist and the social worker. If physical therapy is prescribed, the patients see the same physical therapist again and again. The same social worker sees them repeatedly at their homes and in clinics. When they return to clinics, they see the same physician. If an apparatus is ordered, it is fitted by the physician, who gives full instructions concerning its use and who adjusts it as need arises. The physical therapist sees that the apparatus is properly used, makes any necessary adjustments if she can, or has the patient come to the clinic for this service. If an operation is recommended, the child is not merely turned over to a strange hospital staff. The clinic physician, whom the child knows, performs the operation. A very striking result of this careful, kindly follow-up care is the attitude of patients in the clinic sessions. A child on his first visit is often apprehensive and worried, and manifests his emotions by crying and by resisting the examinations. On subsequent visits, the contrast in the child's demeanor is striking, except in permanently unco-operative children, of whom there are fortunately not many.

Almost 1000 children are now under active clinic care, but there are still almost a hundred towns in the State with a total population of about 160,000, from which no crippled child has yet been admitted to a state clinic. It is reasonable to assume that in many of these rural towns there are crippled children who are in need of care, and the Orthopedic Unit of the Department of Public Health plans to make special efforts to locate them so that they may be offered whatever help they need.

#### DEATHS

COOK—JAMES H. COOK, M.D., of Quincy, died March 28. He was in his fifty ninth year.

A native of Newcastle, Maine, he received his degree from Tufts College Medical School in 1910. He was a fellow of the American College of Surgeons and a member of the Massachusetts Medical Society and the American Medical Association.

His widow, a son, two brothers and a sister survive him.

FREUND—ERNEST FREUND, M.D., of Boston, died recently. He was in his sixty fifth year.

Dr Freund received his degree from the Medical Faculty of the University of Prague. He was a member of the Massachusetts Medical Society and the American Medical Association.

MELEDY—JOSEPH A. MELEDY, M.D. formerly of Milton, died April 1. He was in his fifty first year.

Dr Meledy received his degree from Tufts College Medical School in 1918. He was for many years a physician in the regional office of the Veterans Administration in Boston. He was a member of the Massachusetts Medical Society and the American Medical Association.

His widow survives him.

## MISCELLANY

RÉSUMÉ OF COMMUNICABLE DISEASES  
IN MASSACHUSETTS FOR FEBRUARY, 1942

DISEASES	FEBRUARY 1942	FEBRUARY 1941	FIVE-YEAR AVERAGE*
Anterior poliomyelitis .....	2	0	0
Chicken pox .....	1651	1103	1440
Diphtheria .....	11	6	12
Dog bite .....	489	531	568
Dysentery, bacillary .....	3	12	17
German measles .....	261	89	74
Gonorrhea .....	326	282	346
Measles .....	1755	1896	2244
Meningitis, meningococcal.....	13	6	8
Meningitis, other forms.....	13	†	†
Mumps .....	1930	696	740
Paratyphoid infections.....	4	4	2
Pneumonia, lobar .....	478	461	628
Scarlet fever .....	1399	528	628
Syphilis .....	374	344	413
Tuberculosis, pulmonary.....	240	176	179
Tuberculosis, other forms.....	14	12	19
Typhoid fever .....	6	3	4
Undulant fever .....	5	5	3
Whooping cough .....	780	930	952

\*Based on figures for preceding five years.

†Meningitis, Other Forms (except Pfeiffer Bacillus) not reportable until May 13, 1941.

## GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Anterior poliomyelitis was reported from: Amherst, 1; Boston, 1; total, 2.

Diphtheria was reported from: Cambridge, 1; Everett, 1; Framingham, 1; Lowell, 3; Somerville, 1; Springfield, 1; Waltham, 1; Wilbraham, 1; Worcester, 1; total, 11.

Dysentery was reported from: Tewksbury (State Infirmary), 3; total, 3.

Malaria was reported from: Fort Banks, 1; total, 1.

Meningitis, meningococcal, was reported from: Ayer, 1; Braintree, 1; Brockton, 1; Fall River, 1; Fitchburg, 1; Gloucester, 1; Greenfield, 1; Melrose, 1; New Bedford, 2; Reading, 1; Waltham, 1; Weymouth, 1; total, 13.

Meningitis, other forms, was reported from: Barre, 1; Boston, 3; Brookline, 1; Easton, 1; Fitchburg, 1; Grafton, 1; Marshfield, 1; North Reading, 1; Springfield, 1; Sturbridge, 1; Worcester, 1; total, 13.

Paratyphoid infections were reported from: Boston, 1; Gardner, 2; Quincy, 1; total, 4.

Pellagra was reported from: Boston, 1; total, 1.

Septic sore throat was reported from: Amesbury, 1; Boston, 3; Brockton, 2; Cambridge, 1; Chelmsford, 1; Georgetown, 1; Greenfield, 1; Ipswich, 1; Malden, 2; Merrimac, 1; Newton, 1; Northbridge, 1; Salem, 1; Winchendon, 2; total, 19.

Typhoid fever was reported from: Boston, 3; Lowell, 1; Stoughton, 1; Worcester, 1; total, 6.

Undulant fever was reported from: Ashburnham, 1; Brookfield, 1; Lee, 1; Millbury, 1; Weymouth, 1; total, 5.

Mumps, after showing record-high incidence for the past seven consecutive months, is still at a high level.

Chicken pox, meningococcal meningitis, German measles, poliomyelitis, paratyphoid, scarlet fever, pulmonary tuberculosis and undulant fever were reported at figures above their five-year averages.

Bacillary dysentery, measles, lobar pneumonia, other forms of tuberculosis and whooping cough were reported at figures below their five-year averages.

The focus of animal rabies previously noted in the northeastern section of the State is still active in Middlesex County. Cases were reported from Tewksbury, Lowell and Woburn.

## NOTES

George R. Cowgill, associate professor of physiological chemistry at Yale University and editor of the *Journal of Nutrition*, was recently awarded the \$1000 Mead Johnson and Company prize by the American Institute of Nutrition for researches dealing with the vitamin B complex. The presentation was made to Professor Cowgill by Dr. Albert G. Hogan, professor of agricultural chemistry at the University of Missouri and president of the Institute, at exercises in The Copley-Plaza, Boston.

Dr. Richard P. Strong, professor emeritus of tropical medicine at Harvard Medical School, recently delivered the fifth series of the John Wyckoff Lectures at New York University College of Medicine. The general title was "Tropical Diseases and the War," and at the first lecture, Dr. Strong discussed dysentery, typhus fever and plague, and at the second, trypanosomiasis and onchocerciasis.

## CORRESPONDENCE

## DIPHThERIA ANTITOXIN

*To the Editor:* The Department of Public Health has been distributing diphtheria antitoxin in packages of 1000, 5000 and 10,000 units. Since present opinion favors the administration of at least 10,000 units to all but the very mildest cases of the disease, the department is discontinuing the distribution of the 5000-unit package. When it is desired that only 5000 units be administered, the appropriate amount may be obtained from a 10,000-unit package.

The elimination of this package will also effect economies in the use of paper and glassware, both of which are becoming increasingly difficult to obtain. Because of this increasing scarcity, the department likewise earnestly requests the co-operation of physicians, hospitals and boards of health in the maintenance of all possible economies in the distribution of biologic products. By ordering only the quantities needed for two to four weeks, and by promptly returning all unnecessary surplus stocks, outdated products and empty containers, the department will be greatly aided both in maintaining an adequate supply of needed materials and in effecting economies in the distribution of biologic products. Materials to be returned should be sent to the Antitoxin and Vaccine Laboratory, 375 South Street, Jamaica Plain, Massachusetts.

PAUL J. JAKMAUH, M.D.  
Commissioner of Public Health

State House  
Boston

## REPORTS OF MEETINGS

## BOSTON ORTHOPEDIC CLUB

A regular meeting of the Boston Orthopedic Club was held at the Boston Medical Library on November 17. Colonel Norman T. Kirk, of Washington, D. C., spoke on "The Evacuation and Emergency Treatment of War Wounded." A tentative plan for the management of wounded in a zone of advance includes an aid station for each battalion, a collecting hospital for these stations, a clearing hospital and an evacuation hospital. The first of these can naturally be employed only when the position of the troops is established, not in advance or retreat. *There should be medical troops with each battalion, and*

minimal medical equipment consists essentially of first aid material. Their function is the carrying of the wounded to the collecting station, at which point the task of the medical regiment ends. Thereafter, it becomes the duty of the army to transport the patients.

The progress through the various stations of a hypothetical patient with a compound fracture of the femur was traced. Since all soldiers now receive three prophylactic injections of tetanus toxoid, the administration of tetanus antitoxin is no longer a problem for the first aid station. The first aid pack that each soldier carries contains 90 gr of sulfanilamide, with instructions for its use in compound fractures. Iodine is used around the wound immediately, and an occlusive dressing is applied. A Thomas splint is applied, but no ankle hitch is employed because of the danger of trauma if a long haul is necessary. Blankets are wrapped in a manner designed to lessen the degree of shock. Morphine is administered either on the litter or at the aid station. Sulfanilamide is given orally in doses of 15 gr every four hours until discontinued at some later post, its later use in the wound itself is a matter of choice at these centers. Sodium amylal which has been demonstrated to decrease the degree of surgical shock, may be employed in the future. It has been estimated that proper splinting diminishes the shock of original transit from 50 to 15 per cent. There is not much specific shock therapy at the aid station, except the use of blankets, for heat, and of the Trendelenburg position.

The collecting station is about 1000 yards behind the aid station, and transportation between these points is accomplished by litter only. It has been shown that to traverse such a distance under war conditions of shell fire requires from one to two hours. At this point, there is also very little protection or specific treatment but some segregation of patients can be carried out.

Transportation from here to the clearing hospital three or four miles away, is accomplished by ambulances and requires an hour or more. Advancing troops always have the right of way on the roads and may seriously hamper the evacuation of wounded. Furthermore, there is no ambulance service by day unless air supremacy is certain and patients may thus be forced to wait over in the meager collecting hospitals for as long as eighteen to twenty-four hours. At the clearing hospital, which consists merely of tents, the cases are divided and allocated to their appropriate places. Here also, the first bit of secondary treatment is carried out, such as the repair of splint, and the renewal of dressings. Plasma or serum is administered to patients in extreme shock. An emergency surgical unit associated with this clearing hospital takes care of urgent abdominal, thoracic and head injuries as well as bleeding cases. Amputations are performed on cases that would otherwise be nontransportable. Unfortunately, no operative case can be transferred for six days which is much too long if a retreat becomes necessary. Airplane ambulances are desirable and feasible, but can be applied only after fighters, bombers and transport ship, have been made available in sufficient numbers. No intricate apparatus is employed to evaluate the shock of a patient but clinical diagnosis is relied on.

The wounded are then taken by the army ambulance corps to an evacuation hospital ten to twenty miles in the rear. It was pointed out that because of the rapid change of battlefield trucks rather than trains may become a necessity for the carrying of supplies for such centers in the rear. Each of these hospitals usually has about 750 beds but as many as 2500 cases may be referred to it

during a twenty-four hour period. Segregation of the more urgent is, therefore again necessary. The hypothetical fractured femur is still on the original litter and fixed in the same Thomas splint. Depending on the severity of the injury and the amount of congestion at the hospital, the fracture may be repaired at this point. For mechanical cleansing, there will undoubtedly not be enough water and saline to carry out the desired technique. Therefore, mechanical cleansing takes the form of cutting away all devitalized tissue and removing foreign bodies and bone fragments. Here, for the first time, dried blood and plasma are available for all. More emphasis is being placed on the thorough treatment of simple wounds at this hospital, with the idea of retaining the soldier in the battle area and thus not losing him for the duration so far as that sector is concerned. These wounds are debrided carefully, dusted with sulfanilamide and primarily sutured. Formerly, many such soldiers would either have succumbed to gas bacillus infection or have been lost to their company. This latter fact was considered bad for the morale.

The further treatment of compound fractures is by the Orr method, which comprises the thorough cleaning and debriding of the wound and the immediate application of plaster after the wound has been packed with an impregnated gauze. It is reported that in the recent Spanish war there was only one death from gas infection in over a thousand cases, and that only eight casts were removed because of sepsis. Dr. Kirk offered the objection that most of the patients with gas bacillus infection would have been dead before arrival at this station. Furthermore, the treatment of fractures by this method affords only mediocre results at best, and is not recommended for fractures of the femur. There is evidence that there may be considerable collections of purulent material in joints and soft tissues despite the absence of fever or pain, and this leads to cachexia and chronic debility. It has been concluded by the French observers, therefore, that such treatment of compound fractures is advisable only for short hauls. On the whole, Dr. Kirk believes that plaster is not effective in the stabilization of fractures of the shafts of long bones. Matthews, of London, does not dare use plaster even for short journeys without splitting the cast or making a window, either of which defeats the purpose of this method. Even its staunchest advocates do not use this technique if there is any soft tissue damage, and insist on twenty-four hours of observation before transportation. Some surgeons strongly advocate the use of sulfanilamide locally, whereas others use only vaseline packs. Dr. Kirk favors the use of 10 gm of sulfanilamide locally, packing of the wound, fixation by a Thomas splint or skeletal traction and the continuance of chemotherapy orally. A wound is considered potentially clean only if it is widely debrided and loosely packed.

Statistics reveal that 30 per cent of all injuries are associated with compound fractures—6 to 8 per cent of an infantry division become casualties in each day's fighting, the proportion of killed to wounded being 1:4. Therefore, the number of casualties daily is 900 to 1000 men for each division.

The discussion was opened by Dr. Elliott C. Cutler, who advocated the blood grouping of all soldiers and their congregation in companies according to such groupings. The expert training of the members of the aid station was highly recommended since this is often the place where the most important dressings are carried out. Time is most vital in abdominal injuries, and in thoracic wounds and head injuries. The last are apparently decreasing with the diminishing use of trucks in actual

warfare. It was warned that many more wounded will of necessity be left in the field with the increasing mobility of war, for they cannot be transported fast or far enough with trucks. The use of plaster, for transportation only, was urged as a means of comfortable and easy removal. It was pointed out that chloroform is an ideal anesthetic for healthy young men: it has a rapid induction and recovery, is of small bulk, and is good in the desert or on ship-board.

Dr. G. W. Taylor stated that intravenous anesthesia may be the answer to that problem, at least partially. He expressed some dissatisfaction with the reported results of the Orr method of treating compound fractures.

Dr. R. C. Cochrane believes that splints give good immobilization, with a minimal amount of shock. Although army regulations are admittedly necessary in the front hospitals, some allowance for variation in technic should be made in the evacuation and general hospitals. Plaster as a means of immobilization for short hauls may be acceptable, but it becomes particularly dangerous for any prolonged period because of the lack of signs and symptoms in the event of sepsis.

Dr. O. J. Hermann read excerpts from letters of Dr. Charles Bradford, in England, which indicate that the Orr method is gaining wide acceptance even among men who saw and used other methods, but that it is not used blindly in every case. For the treatment of shock, strategically placed stations permit rapid delivery of all types of blood. There has been some trouble with the coagulants in plasma. Serum has proved effective, especially in the initial treatment of burns. For anesthesia, nitrous oxide, oxygen and ether and chloroform are still being widely used. Nitrous oxide is good for chest surgery, especially in avoiding complications. Pentothal may supplant some of these for shorter procedures.

In conclusion, Dr. Kirk stated that although chloroform is a good, safe anesthetic in competent hands, there are not enough such trained men. Nitrous oxide, oxygen and ether is being used in Egypt with great success. Plasma has been used extensively at the Walter Reed Hospital, with no reactions. The Roger-Anderson method for the treatment of fractures has fallen into disuse in the army because of the incidence of osteomyelitis and the failure to control the pain adequately. Furthermore, there is not the free motion at the joint that is so widely publicized, for the fixation pushes the surfaces together.

#### UNITED STATES NAVAL HOSPITAL

At a regular meeting at the United States Naval Hospital in Chelsea on January 9, Dr. Francis T. Hunter, recently of the Massachusetts General Hospital and now a member of the Medical Corps of the United States Naval Reserve, spoke on "Transfusions." The discussion was confined to some of the difficulties with and the new developments in the use of blood and its substitutes. Dr. Hunter added that the Army and Navy are now typing the blood of all men in the armed forces and attaching an identification tag with this information to each individual, the Landsteiner method of nomenclature being employed.

Some of the possibilities of blood typing in legal medicine were pointed out. If one parent is Group AB and the other is Group O, all the children will be either Group A or B. Another corollary of this rule is that if either parent is Group AB, there can never be any children with Group O. Infants can be typed immediately after birth, for the agglutinogens of the human cells are present

early in fetal life; however, the agglutinins of the serum may not be detectable for several months or even a year, so that infants may occasionally receive blood of other types without mishap. Subgroups 1 and 2 of Group A are often blamed for reactions and deaths, but there is as yet no good evidence that they are clinically significant. All groups have Subgroups, m, n or mn, which seem to be unimportant for transfusion purposes but may help in medicolegal problems.

Since the agglutinins of serum are destroyed by bacterial contamination, test serums should be discarded after one week. One should also be careful of the cleanliness and the type of glassware, since serum deteriorates in the presence of alkali. If test serum is being made by an institution, care should be taken to titrate the serum before pooling, and only high-titer serums should be employed—otherwise, incompatibilities may not be detected in typings. Lecithin has proved a valuable aid in ruling out pseudoagglutinations due to rouleaux formation. By placing a small amount of this substance, which increases the surface tension of the cells and prevents the formation of biconcave disks on the slide, rouleaux formation is avoided. This occurs primarily in acute infections or in any person with an increased sedimentation rate. If any doubt of the compatibility of donor and recipient of the same type remains after all the usual measures have been tried, 20 cc. of blood from the donor may be injected into the recipient; the rest of the transfusion can be safely given if there is no reaction within twenty minutes.

It is reported that, when all known causes of transfusion reactions have been removed, there are still slight temperature elevations in from 25 to 50 per cent of recipients. But if the blood is taken when the donor is fasting, these slight febrile reactions are reduced to about 3 per cent; furthermore, this results in a much smaller number of other allergic reactions. Reactions from unclean apparatus are now rather a minor consideration. One final warning is for the person taking the blood to make sure that the donor is who he is supposed to be, for such errors have led to lawsuits.

Dr. Hunter then discussed blood banks and blood substitutes. The former are expensive and troublesome, but are of value in communities where there is no supply of readily available donors. Even when refrigerated, whole blood changes with time and especially under conditions that increase the number of enzymes. All these factors favor laking of the erythrocytes, and free hemoglobin in the circulating blood causes changes of the renal tubules that may be fatal—incidentally, these changes are similar to those of arsine gas poisoning, which apparently causes laking of the circulating erythrocytes. Agitation also lakes red blood cells, and this factor has made traveling blood banks for armed forces impracticable. The best blood bank is that provided by the men in service, with type tags attached, in whom the freshness of the blood is ensured.

Plasma will never completely replace whole blood, for erythrocytes are eventually necessary in most cases. It is better than whole blood in burns, because of the hemoco-concentration, but has not proved so beneficial in nephrosis as had been hoped. Liquid plasma obtained from the deteriorating blood of blood banks apparently lasts only about nine months, whereas dried plasma seems to stay unchanged for as long as five years. The latter product is now available on the market for \$26.22 for the equivalent of 250 cc. of liquid plasma, which is equal in osmotic effect to a 500-cc. whole-blood transfusion and is therefore not very expensive. The beef albumin of

Cohn appears very promising, he has already removed the beef antigens and is rapidly finding methods for removing other impurities. This may be a cheap blood substitute and may outmode all others as a temporary expedient. This is another argument against investing large amounts of money in blood banks at the present time.

The following points were brought out by Dr Hunter in the discussion. Although it may be possible to use Group O donors with impunity, in many cases, occasionally in recipients who have had either no previous transfusions or one from another type, it is not wise to give multiple transfusions from a so-called universal donor, for, in certain cases, there may be a temporary heightening of the agglutinin titer and a true and serious reaction of incompatibility. If one must employ this type, it is advisable to take serum for direct matching from the recipient between each transfusion.

The early and unmistakable signs of kidney shutdown from an incompatible transfusion reaction are renal pain, cyanosis, chest pain and dyspnea. These occur almost immediately, and reactions after three or four hours are usually attributable to some foreign protein from the apparatus or donor. Decapsulation for renal failure will probably not prove efficacious, if the experience at the Massachusetts General Hospital is any criterion, for it has been shown that such a kidney puts out less urine than its nondecapsulated mate. Alkalinization of such patients is logical, for hemoglobin is more soluble at a high pH. This will probably not result in the solution of crystalline material, in the kidney tubules, but may prevent the further precipitation of hemoglobin.

## BOOK REVIEWS

*Diseases of the Nails*. By V Pardo-Castello MD. With a foreword by Howard Fox, MD. Second edition. 8°, cloth, 193 pp., with 94 illustrations. Springfield, Illinois: Charles C Thomas, 1941. \$3.50.

The manifestations of disease in the nails are puzzling to most physicians. This book should therefore be a welcome addition to any medical library, whether of the individual physician or of the medical school or hospital.

The text of this edition has been definitely improved. Emphasis has been placed on the numerous general diseases in which nail changes may occur, as well as on affections peculiar to the nails. The histology and pathology are discussed rather briefly, but an excellent feature of the book lies in the many and excellent photographs, which add so much in the assimilation of the text. Attention should be called to two valuable tables—one regarding the occupations with characteristic nail changes and the other listing changes caused by poisons. An extensive bibliography and numerous excellent illustrations add much to the value of this book.

*Teaching Preventive Medicine to Medical Students, with Special Reference to the Use of Health Department Facilities*. By Hugh R Leavell, MD, DPH. 8°, paper, 77 pp., with 9 tables. New York: The Commonwealth Fund, 1941. 25c.

A discussion of the use of health-department facilities for teaching preventive medicine to medical students is timely, since this is one of the more recent suggestions in the field of public health, and one that has already been tried out in many medical schools. The material reported was gathered by the questionnaire method, and has been sifted by an author who is obviously familiar with the difficulties faced by both medical schools and

health departments. It is of particular interest to those concerned with this phase of medical education, and has many tables and comments that may be of interest to others. It is a carefully prepared and worthwhile statement of the subject for 1941, and one hopes that a comparable study in 1951 not only will be made but will show a natural growth of this potentially valuable method of instruction.

*The Therapeutics of Internal Diseases*. Supervising editor: George Blumer, MD. Associate editor: Albert J Sullivan, MD. Three volumes. 8°, cloth. Vol I 872 pp., 136 illustrations, with 26 tables and 1 chart. Vol II 1042 pp., with 2 charts and 14 tables. Vol III 738 pp., 39 illustrations, with 1 chart and 2 tables. New York: D Appleton Century Company, 1941. Sold only as a set, \$40.00.

In these days, when the literature on any detail of medicine has become so voluminous it is impossible for any physician to make inquiry with satisfaction among the many interesting scattered findings and advances in the field of therapeutics. Indeed, the literature increases so rapidly over the field as a whole that one is forced to retreat in blind confusion. To overcome this situation, compilations of what known as reference books are published. Even if a penitential search through a series of reference works consumes time, it remains, so far, the most satisfactory method of obtaining information of various kinds from competent authority. Further elaboration can be pursued from reference literature.

With this in mind, one can consider the worthy enterprise edited by George Blumer. Volume I contains the following splendid sections on 'Nutrition and Dietetics' (A Smith), 'The Principles of Endocrine Therapy' (K W Thompson), 'The Principles of Serum and Vaccine Therapy' (M Eaton), and 'Specific Therapeutic Techniques' (W J Bruckner). Unfortunately, this helpful material is sandwiched among some four hundred pages of questionable therapeutic procedures from spa therapy through a galaxy of peculiar methods of various forms of physical therapy. This section on physical methods is muddled and poorly planned, and merely adds to the confusion already present in physical therapy, emphasizing its lack of physiologic background.

Perhaps the most important and best presented section is in Volume II. The four hundred and fifty-four pages dealing with pharmacology, therapeutics and toxicology, written by Louis S Goodman, stand well above the rest of the sections and form the bulwark for the entire edition. The section on virus diseases (J R Paul, G Klatskin and M E Howard) is a dried extract withdrawn from already present standard reference material and reveals the stigmas of resemblance with some face lifting to other compilations. Thus, this section, which should be of great interest today, reveals none of the remarkable interrelations among virus diseases. In the same volume, the sections on Rickettsiae (Blumer), and more especially the mycobacterioses (E N Packard, H E Hasseltine and W T Longcope), the bacillary infections (J H Musser and P H Jones, Jr), and the coccid infections (M Finland, C S Keefer and E H Place) are superb analyses and dissertations.

Volume III includes a chapter on diseases due to fungi (D T Smith), a remarkably capable section by Faust on metazoan diseases and, no less interesting, a precise chapter by Craig on protozoan diseases. These sections show careful review and study and include material on intoxications (Blumer). The section on diseases of physical

agents is incomplete, and the authors (E. Lawrence and H. Martland) fail to elucidate from a physiologic standpoint the nature and treatment of accidental electrical injuries. Seasickness is not linked up with any of the important work done in Britain on this subject. However, this part of the volume is offset by reliable sections on the treatment of diseases of the lower respiratory tract (D. S. King), the treatment of diseases of the blood and lymph vessels (I. S. Wright), and the treatment of heart disease and heart failure (H. M. Marvin).

On the whole, the three volumes represent the time-consuming editorial efforts of Dr. Blumer, who with great care has attempted to assemble data pertinent to therapeutics; indeed, it is today the best of its kind for its comprehensive scope.

---

*Observations Made during the Epidemic of Measles on the Faroe Islands in the Year 1846.* By Peter L. Panum, M.D. 8°, cloth, 111 pp. New York: published by the Delta Omega Society and distributed by the American Public Health Association, 1940. \$2.50.

In the year 1846, an epidemic of measles in the Faroe Islands offered an exceptional opportunity for the study of the disease. The population was scattered, sparse and virtually nonimmune, since measles had not appeared there for sixty-five years. Moreover, no other eruptive fever was present to confuse the issue. The conditions possessed "the potentialities of a vast experiment." But successful experiments require sharp observations, imagination and an open mind. These Panum had; and the man and the occasion met. The result is one of the classics of epidemiology.

Up to this time, as Dr. Doull points out in his introduction, it was still believed that, although measles was usually spread by direct contact, it might sometimes arise spontaneously, and the notion of a *contagium vivum* as the cause was held by very few. It was supposed that the disease was most readily transmissible in the desquamative stage, and estimations of the incubation period varied widely.

Panum settled the fact once and for all that the exanthem appeared with great regularity thirteen or fourteen days from the effective exposure, which meant that the disease was transmitted "at precisely the time that the exanthem was breaking out or had just broken out." He said nothing of infectivity prior to the eruption, although some of his histories indicated it. He doubted, if he could not prove, that the disease was not transferable in the post-eruptive period. He himself observed no instance of transmission by fomites. He offered, it is true, no explanation of how the infectious material is passed out of the body; indeed, he hazarded no opinion concerning the nature of the morbid agent. Regarding spontaneous origin, he could only say that it did not occur in the Faroe Islands. Nevertheless, his work will stand for all time, and it is most fitting that it should be published in this handy translation.

---

*The Pharmacology of Anesthetic Drugs: A syllabus for students and clinicians.* By John Adriani, M.D. Second edition. 4°, cloth, 86 pp., with 102 illustrations. Springfield, Illinois: Charles C Thomas, 1941. \$3.50.

There has always been a real need for a book of this type, which correlates clinical anesthesia with the pharmacology and physiology of the drugs in current use, for both the clinician and the medical student. Indeed, it is a book well worth reading to refresh one's mind on the

action of the lethal drugs used outside the field of anesthesia.

The author has accumulated his data from numerous observations and personal experiments. The material is presented in an honest, scientific manner, with the thought that the facts presented might serve as a guide until further investigation may be obtained. The subject matter is uniquely arranged in diagrammatic fashion, to focus attention on the physiologic and pharmacologic changes occurring with the various organs and systems of the human body, so that further study and interest in the fundamental sciences associated with anesthesiology may be stimulated.

The subjects covered include general properties and chemical natures of anesthetic drugs, general systemic effects on the respiratory, circulatory and central nervous systems, and disturbances of respiration including oxygen and carbon dioxide transport, oxygen want and the physiologic and toxic effects of carbon dioxide.

The various anesthetics include gaseous agents (nitrous oxide, ethylene and cyclopropane), volatile agents (ethyl ether, divinyl oxide, chloroform and ethyl chloride), non-volatile agents (bromethanol with amylene hydrate [Avertin], trichlorethanol and paraldehyde), barbiturates, local anesthetics and opiates. The nonanesthetic drugs used in conjunction with anesthesia are also discussed. In the last chapter, some clinical considerations are presented, such as preanesthetic medication, technics of administration, carbon dioxide absorption, complications and accidents, anesthetic and respiratory complications, and the explosibility of anesthetics. There is also a brief bibliography, which covers more recent contributions to this field of medicine.

---

*Clinical and Experimental Investigations on the Genital Functions and Their Hormonal Regulation.* By Bernhard Zondek. 8°, cloth, 264 pp., with 59 illustrations and 44 tables. Baltimore: Williams and Wilkins Company, 1941. \$4.50.

Many of the advances in knowledge of the sex hormones are associated with the name of Zondek. The author includes in this short monograph a résumé of his lifework with sex hormonology, as well as a review of the work by other investigators that corroborates his findings. This volume is of monumental scope, and bears witness to his intense pursuit of facts. Typical of the pure scientist are his experiments with water from the Dead Sea. All layers of the sea were analyzed, and it was found that the water and sludge at the bottom contain large amounts of estrogenic substances, whereas other layers have little or none.

The chapter entitled "Fate of Sex Hormones in the Organism" shows that naturally occurring estrogens are rapidly destroyed in the body, whereas synthetic estrogens (Stilbestrol) are very slowly destroyed. This accounts, perhaps, for the powerful and often toxic action of the latter. Evidence is presented to show that the corpus luteum hormone can produce bleeding of the uterine mucosa alone, whereas it had been supposed that this was possible only in a mucosa previously prepared by the action of estrone. On the basis of present knowledge, an interesting and plausible theory for the menstrual cycle is advanced.

Many of the facts presented in this volume will form the basis of future clinical experiments. The book makes interesting reading for both the practitioner and the investigator, because the author deals throughout with clinical and animal experiments.

# The New England Journal of Medicine

Copyright, 1942, by the Massachusetts Medical Society

VOLUME 226

APRIL 16, 1942

NUMBER 16

## THE RELATION OF TANNIC ACID TO THE LIVER NECROSIS OCCURRING IN BURNS\*

DONALD B. WELLS, M.D.,† HENRY D. HUMPHREY, M.D.,‡ AND JAMES J. COLL, M.D.‡

HARTFORD, CONNECTICUT

THE phenomena associated with severe burns follow each other in a more or less orderly and well-defined chronologic sequence.<sup>1</sup> Death may result almost immediately from overwhelming trauma. Most burned patients are seen in primary reflex shock, a state of marked vascular vasodilatation caused by fright and pain. Primary reflex shock may blend rapidly and almost imperceptibly with so-called "secondary shock," which, with its increasing capillary permeability and massive fluid shift or loss, may be fatal within forty-eight hours. What we are accustomed to calling "toxemia" ensues; however, the use of the adjective "toxic" to describe a patient in poor condition from undetermined causes is certainly no proof that a toxin exists, and belief in a "toxemia" in burns may well arise from the clinician's bewilderment in the face of potent factors that he cannot readily catalogue. It is interesting that no less than twenty substances purporting to be the "burn toxin" have been listed<sup>2</sup> but no specific histopathology for burns has ever been described. Infection is usually a comparatively late stage in the chronologic sequence; but in three or four days, if severe sepsis develops, it may overshadow the whole clinical picture.

Ten consecutive autopsies recently performed in cases of death from burns at the Hartford Hospital serve to illustrate this sequence of events. Two of these patients died from direct trauma within two to four hours after injury; another died of shock or fluid imbalance eleven hours after the injury; 4 more died of "toxemia" ninety-three to one hundred and twenty hours following the injury; another, admitted late, died of infection one hundred and twenty hours after the injury, a blood

culture on admission showing hemolytic streptococci; the last 2 died of complications, 1 fifty-five hours after the accident from the result of an associated cerebral laceration sustained in an airplane crash, and 1 of a cerebral glioma thirty-three days after admission—the glioma was probably the cause of the convulsive seizure during which this patient was burned. The 4 patients who died of "toxemia" are of particular interest, and their cases are briefly presented below because each one exhibited central lobular liver necrosis as an outstanding lesion or as the sole cause of death. Treatment of these patients followed the general principles laid down by one of us<sup>3</sup>: the employment of a tannic acid tub in which a careful débridement was done without an anesthetic, a thin, sterile tan being secured in every case; the tan was subsequently maintained by the use of a tannic acid spray, and for the most part was kept perfectly dry by a current of warm air from a commercial hair drier; intravenous glucose in physiologic saline solution was given in adequate quantities; each patient received whole-blood transfusions; and intranasal oxygen was employed.

### CASE REPORTS

CASE 1. R. W. (H. H. 338,316), a 17-year-old boy, was admitted on July 1, 1937. Practically all his clothing had been burned off when a can of gasoline he was holding became ignited from a bystander's cigarette. The burns were estimated to involve not less than five sixths of the entire body surface. The patient was immediately put in a tub of tannic acid solution, the loose skin removed, and the hair shaved. He remained in the tub 4½ hours and, after being transferred to bed, was sprayed repeatedly with a tannic acid solution and immediately dried with a commercial hair drier. Intravenous glucose and three whole-blood transfusions were given. Continuous intranasal oxygen was started 18 hours after admission. The patient was spontaneously responsive during most of his stay in the hospital, but became increasingly restless and irrational after the 63rd hour, when the blood nonprotein nitrogen was 128 mg. per 100 cc. and the hemoglobin 111 per cent. Death occurred 91 hours after admission.

\*Presented at the annual meeting of the New England Surgical Society, Hanover, New Hampshire, September 5, 1941.

†From the Department of Surgery and the Department of Pathology, Hartford Hospital.

‡Visiting surgeon, Hartford Hospital.

§Resident intern in pathology, Hartford Hospital, assistant in pathology, Yale University School of Medicine.



*Autopsy.* The body was that of a well-developed and well-nourished boy. At least five sixths of the body surface was covered with a firm, dry tan without evidence of infection. There was marked congestion of the viscera, with scattered petechiae, and blood-tinged fluid was present in the body cavities. There was no ulceration of the duodenal mucosa. The liver weighed 1960 gm. and showed no gross changes. The gall bladder and bile ducts were not unusual.

On microscopic examination, all organs except the liver showed nothing but cloudy swelling and congestion. In the central two thirds of the liver lobule, the parenchymal cells showed a granular, deep-pink-staining cytoplasm in contrast to the relatively normal cells in the peripheral area. Throughout this central zone, the nuclei were slightly enlarged, and there were numerous necrotic foci (Plate 1, *A*). A moderate number of mitoses were present in the peripheral zone (Plate 1, *B*). The sinusoids were distended with blood. There was no leukocytic infiltration.

*Comment.* This case showed a combination of early liver necrosis and vascular failure. The latter was probably the greater lethal factor.

CASE 2. N. N. (H. H. 357,822), a 23-year-old man, was admitted on August 18, 1938. An electric flash in a transformer room had ignited his clothing. The entire head, the torso to the waistline, both upper extremities and wide patches on both thighs, both anteriorly and posteriorly, were burned. The patient was put in a tub of tannic acid solution and carefully and thoroughly débrided. He remained in the tub  $2\frac{3}{4}$  hours. This treatment was followed by repeated spraying with a tannic acid solution, which was immediately dried with a commercial hair drier. Three transfusions were given, and no gross fluid imbalance was clinically apparent until the last 24 hours of life, when edema of the lower extremities developed. About 2 hours before death, the patient became restless, complained of severe pain in the upper abdomen, and vomited several times. He died 96 hours after admission.

*Autopsy.* The body was that of a well-developed and moderately overnourished young man. The burned areas were covered by a firm, dry, noninfected tan. The tissues were moist and moderately icteric. A moderate amount (200 cc.) of slightly bloody fluid was present in the body cavities. The viscera showed moderate congestion, with scattered petechiae. The liver weighed 2000 gm., and the cut surface showed a fine mottling, with hemorrhagic points. The gall bladder and biliary ducts were not unusual. No ulceration of the duodenal mucosa was found.

On microscopic examination, except for multiple small thrombi in the lungs and congestion and cloudy swelling of other viscera, significant histologic changes were limited to the liver. The central three fourths of the liver lobules showed extensive hemorrhagic necrosis, with complete disruption of the cords of liver cells (Plate 1, *C*). A few cells in the peripheral region were still intact, and some of these were in mitotic division. A slight diffuse infiltration of polymorphonuclear leukocytes was present throughout, together with a scattering of fat globules. There was no increase in fibrous tissue.

*Comment.* Although the changes present in this case suggested vascular failure, the picture was dominated by the liver necrosis.

CASE 3. K. W. (H. H. 388,162), a 23-year-old man, was admitted on April 26, 1940. An explosion of illuminating gas had resulted in burns involving the entire face and neck, upper chest, back and both arms except for the

palms of the hands. The patient was immediately put in a tub of tannic acid solution, where a thorough débridement was carried out. He remained in the tub for  $2\frac{1}{4}$  hours. After being removed, he was repeatedly sprayed with a tannic acid solution and immediately dried with a commercial hair drier. Intravenous glucose and two whole-blood transfusions were given. For the first 72 hours, the general condition remained satisfactory, and the patient sat up in a chair for several brief periods. Sixty-four hours after admission, the blood chlorides were 428 mg., and the serum protein 6.7 gm. per 100 cc. Eighty-four hours after admission, there was clinical jaundice; the red-cell count was 4,900,000, with a hemoglobin of 104 per cent (16 gm.), the chlorides 425 mg. per 100 cc., the carbon dioxide combining power 56 vol. per cent, the serum van den Bergh (positive, direct) 23 units (115 mg. bilirubin per liter), and the serum protein 6.8 gm. per 100 cc. No clinical improvement was observed after the repeated use of Eschatin. The patient became increasingly stuporous, with a rising temperature and pulse. The urinary output was satisfactory throughout his course in the hospital. Death occurred 110 hours after admission.

*Autopsy.* The body was that of a well-developed and well-nourished young man. The burned areas showed a firm, dry tan without evidence of infection. All the tissues were moist and moderately icteric, and the body cavities contained a small quantity of bile-tinged fluid. The lungs were not remarkable except for slight edema and congestion. The heart, gastrointestinal tract, spleen, pancreas, adrenal glands and kidneys showed no gross anatomic changes. There was no ulceration of the duodenal mucosa. The liver weighed 1240 gm., and was soft and flabby. The cut surface revealed a finely mottled red-and-yellow appearance. There was dark thick concentrated bile in a small thin-walled gall bladder. The bile ducts were not remarkable and contained thin, clear bile.

Microscopic examination showed no histologic changes in any of the organs except the liver. There was extensive central hemorrhagic necrosis involving more than three quarters of the liver lobule, with disruption of the liver cords. Only a narrow zone of intact cells remained in the peripheral areas. These cells varied markedly in size and staining reaction. Many had large nuclei, with irregularly clumped chromatin. Mitotic figures were present, some of which were bizarre forms with scattered chromosomes. Definite evidence of regeneration was not demonstrated. Fat globules were present in slight degree through the area of necrosis and in the remaining liver cells. A moderate number of polymorphonuclear leukocytes infiltrated the interstitial tissue.

*Comment.* In this case, death was due solely to liver necrosis.

CASE 4. W. L. (H. H. 396,523), a 26-year-old man, was admitted on September 18, 1940. While the patient was working under his own car, a pan of gasoline caught fire and the flames spread to his clothing. He walked to the hospital. Diffuse burns involved the left side of the face, neck, chest, whole left upper extremity and the fingers of the right hand. The patient was put immediately in a tub of tannic acid solution and débrided. He remained in the tub  $4\frac{1}{2}$  hours. This treatment was followed by repeated spraying with tannic acid solution, which was immediately dried with a commercial hair drier. Intravenous glucose and two whole-blood transfusions were given. Fifteen hours after admission, the red-cell count was 5,060,000, with a hemoglobin of 97 per cent (15.0 gm.). Sixty-eight hours after admission, there was clinical jaundice, with an icteric index of 53. Ninety-one hours



PLATE 1. Human Liver Lesions Following the Administration of Tannic Acid for the Treatment of Burns.

A. Case 1. Early central necrosis (hematoxylin and eosin  $\times 100$ ).

C. Case 2. Advanced hemorrhagic central necrosis (hematoxylin and eosin:  $\times 85$ ).

B. Case 1. Higher magnification of A, showing mitoses and other nuclear changes (hematoxylin and eosin:  $\times 420$ ).

D. Dr. Helsen's case. Intermediate central necrosis (hematoxylin and eosin:  $\times 85$ ).

after admission, with a normal temperature but rising pulse, the nonprotein nitrogen was 80 mg. per 100 cc., the blood chloride 406 mg., the carbon dioxide combining power 54 vol. per cent, the serum protein 6.4 gm. per 100 cc., and the icteric index 100. The patient died 121 hours after admission.

**Autopsy.** The body was that of a well-nourished and well-developed young man presenting diffuse, satisfactorily tanned burns. There were slight generalized edema and moderate jaundice. The pericardial cavity was entirely obliterated by dense adhesions. The heart weighed 500 gm. Each pleural cavity contained about 200 cc. of bloody fluid. Each lung showed slight edema, and in the lateral portion of the left lower lobe, there was an area of pneumonic consolidation about 10 cm. in diameter. The peritoneal cavity contained 300 cc. of yellow fluid. There were hemorrhagic areas throughout the intestinal tract, but no ulceration. The liver weighed 2390 gm. There were multiple areas of subcapsular hemorrhage. The cut surface was a pale yellow brown, with small hemorrhagic areas throughout. The gall bladder and bile ducts were not remarkable.

On microscopic examination, the pulmonary areas of consolidation showed a characteristic pneumonic picture. The kidney tubules showed cloudy swelling. Almost the entire liver lobule was involved in hemorrhagic necrosis. Only in small foci in the periportal areas were intact cells present, and mitoses were infrequent. Slight diffuse leukocytic infiltration was present. Fat globules in moderate amount were noted in both necrotic and viable tissue. There was very little evidence of bile stasis.

**Comment.** The liver necrosis, which was the most massive of all the cases, was complicated by lobular pneumonia, inactive rheumatic heart disease and vascular failure.

Another case was brought to our attention by Dr. Milton Helpert, assistant medical examiner of New York City. A thirteen-month-old boy was severely scalded over the face, trunk and extremities. The local treatment was tannic acid and silver nitrate. The patient died eighty-two hours after the burn was sustained. The following description of the liver is quoted through the courtesy of the New York Hospital and the Department of Pathology, Cornell University Medical College (N. Y. H. 246,442, Necropsy 9780):

**Gross.** The liver weighs 340 gm. The organ is of normal shape; it is firm but shows a moderate yellow discoloration. The central parts of the lobules are red.

**Microscopic.** In the central half of the lobule, the liver cells are more pale-staining than in the peripheral half [Plate 1, D]. The nuclei of many liver cells are pyknotic, and some cells contain no nuclei. Some of the liver cells are eosinophilic. The liver cells in the peripheral half contain many fat vacuoles but are otherwise normal.

Until a few years ago, it could be truthfully stated that there are no internal or visceral lesions pathognomonic of burns and scalds.<sup>4</sup> Only recently has a specific histopathologic lesion in the liver been reported following certain severe burns. This lesion is so striking that, had it been present in earlier cases, it could not possibly have been overlooked by the army of clinical and experi-

mental observers who have studied burns. In 1938, Wilson, Macgregor and Stewart<sup>5</sup> first described the appearance of the liver as follows:

On naked eye examination, the liver was slightly enlarged, light yellow, soft, greasy and friable. On the cut surface, the lobular marking was conspicuous owing

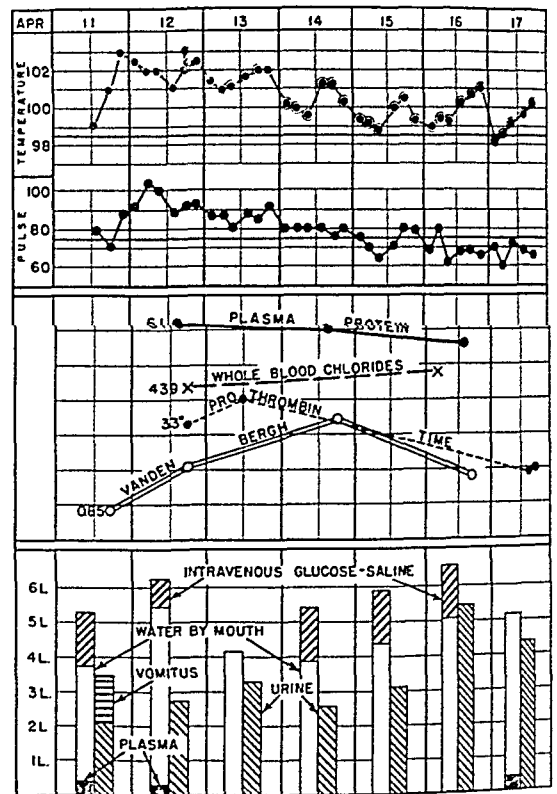


FIGURE 1. Diagrammatic Summary of Data in Case 5.

to greater pallor of the central zone; sometimes, however, haemorrhage in the central zones produced an appearance resembling "nutmeg" liver. On microscopic examination, necrosis of varying degree of the cells of the central parts of the lobules was seen. In the most extreme examples only a narrow strip of liver substance surrounding each portal tract showed surviving liver cells; the remainder were completely necrotic.

Similar cases at necropsy have been reported by Belt,<sup>6</sup> McClure,<sup>7</sup> Buis and Hartman<sup>8</sup> and others. This striking liver lesion has heretofore been attributed to toxemia or anoxia.

Furthermore, we have seen, and others have reported, human beings with burns treated with tannic acid who have shown definite clinical and chemical evidence of liver damage but have recovered. The following case is typical:

**CASE 5.** R. G. S. (H. H. 407,654), a 15-year-old boy, was stamping out a smoldering tree stump when it burst into flame and ignited his clothing. Burns involved both upper extremities, the left chest and axilla and the right lower extremity. Within 24 hours, there was evidence of liver damage, as indicated by the van den Bergh test and by the prothrombin time, which reached a maximum in 72 hours and then subsided (Fig. 1); the boy recovered, and was discharged from the hospital on the 18th day.

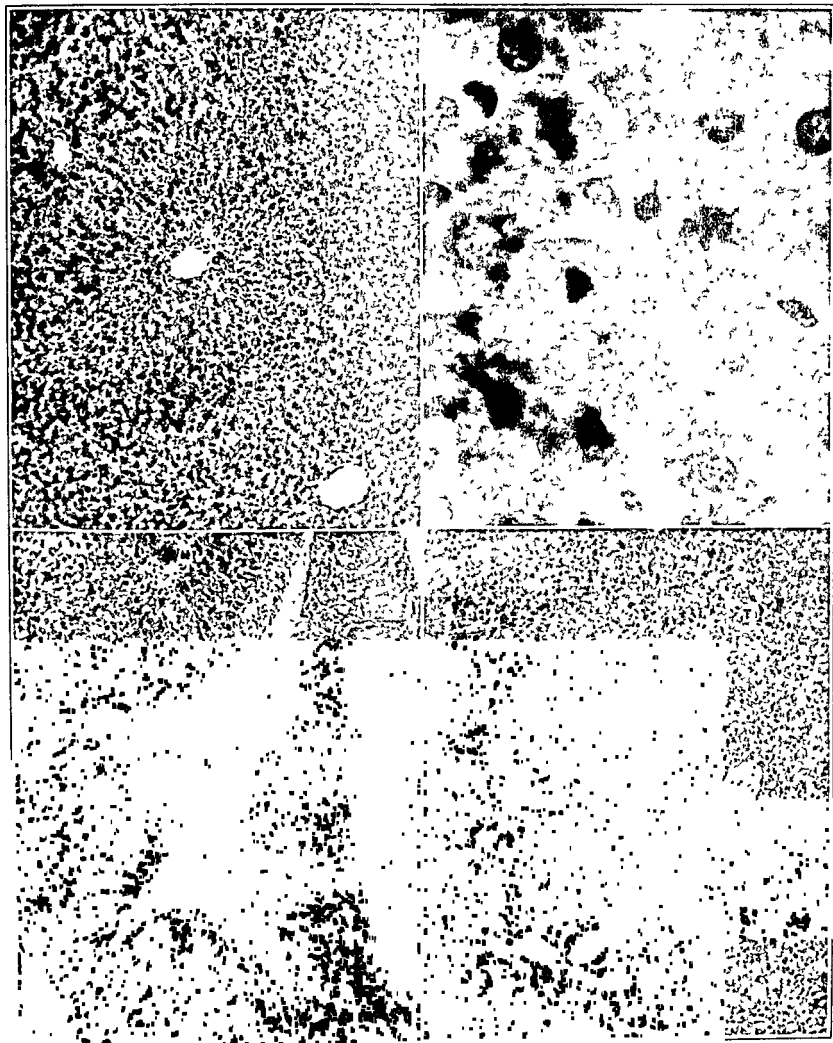


PLATE 2. *Experimental Liver Lesions in Rats Following the Administration of Tannic Acid.*

- A. Experiment 15 (Rat 6). Moderate central necrosis after 0.1 mg. tannic acid (hematoxylin and eosin  $\times 100$ ).  
 B. Experiment 15 (Rat 6). Higher magnification of A, showing mitoses and other nuclear changes (hematoxylin and eosin:  $\times 880$ ).  
 C. Experiment 17 (Rat 4). Moderate central necrosis after 0.2 mg. tannic acid (hematoxylin and eosin:  $\times 75$ ).  
 D. Experiment 17 (Rat 1). Advanced central necrosis after 0.2 mg. tannic acid (hematoxylin and eosin:  $\times 95$ ).

On review of the reported cases and particularly the proved cases coming to necropsy, the common denominator appeared to be that tannic acid had been employed in the treatment. Because it seemed to be of interest to investigate the possible role of tannic acid in the production of liver damage, a series of experiments was planned

tion sites employed. All other organs examined presented a normal appearance except for a slight cloudy swelling. No significant variation in the findings between the rats on either of the specified diets was observed.

The liver damage produced by these injections of tannic acid solution was characterized by: ne-

TABLE 1. Summary of Rat Experiments.

EXPERIMENT No.	No. of RATS	DOSAGE OF TANNIC ACID						RAT KILLED	EVIDENCE OF LIVER DAMAGE				REMARKS
		STRENGTH OF SOL.	FIRST DAY		SECOND DAY		TOTAL DOSAGE		MITO- SIS	NECRO- SIS	HEMOR- RHAGE	IN- FLAM- MATION	
			%	cc.	cc.	cc.							
HOUSE DIET													
5	7	5	1.0				0.05	4th	±	±	0	0	
8	6	10	1.0				0.10	4th	±	+	0	0	
10	6	10	1.0	1.0			0.20	3rd	+	++	±	±	
12	6	10	1.0	1.0	1.0	1.0	0.40	3rd	++	+++	++	+	
STANDARD DIET													
15	6	5	1.0	1.0			0.10	3rd	+++	++	±	±	
16	6	5	1.0	1.0	1.0		0.15	3rd	++	+++	+	+	
17	6	5	1.0	1.0	1.0	1.0	0.20	3rd	+	+++	+	+	1 died within 24 hr.; another within 48 hr.
18	6	5	1.5	1.5			0.15	3rd	+	++	+	±	1 died within 48 hr.
19	6	5	1.5	1.5	1.5		0.23	3rd	+	+++	+	0	1 died within 24 hr.
20	6	5	1.5	1.5	1.5	1.5	0.30	3rd	+	+++	++	+	1 died within 48 hr.
21	6	5	1.0	1.0	1.0	1.0	0.20	3rd	++	++	+	+	
22	6	5	1.0	1.0	1.0	1.0	0.30	3rd	+	+++	+	+	1 died within 48 hr.
23	4	5	1.0	1.0	1.0	1.0	0.40	3rd	+	+++	+	±	1 died within 48 hr.

to determine the effect of subcutaneous injections of tannic acid on the liver in rats.

Albino rats weighing 70 to 90 gm. were selected. They were maintained on specified diets—one group on a house diet of raw bacon, lettuce, bread and grain, and the other on a standard diet of casein, sucrose, salts, cottonseed oil, cod-liver oil and brewers' yeast—for a week or more before being used, as well as throughout the period of experimental observation. Tannic acid (Mallinckrodt, U.S.P., fluffy) was employed. Subcutaneous injections of a 5 or 10 per cent solution of tannic acid were given in doses that did not exceed 1.5 cc. at any one site, to avoid leakage and to facilitate absorption. No anesthesia was used. Rats that survived were killed on the third or fourth day by a blow on the head. The tissues were fixed by formalin or Zenker's fluid, and suitable sections were stained with hematoxylin and eosin.

The rats were injected, usually in groups of 6, with varying amounts (0.05 to 0.40 gm.) of tannic acid in from one to eight sites over a period of forty-eight hours (Table 1). Of the 77 rats injected, 8 failed to survive. Every one of the remainder showed some degree of liver damage, which, in general, varied directly with the amount of tannic acid injected and the number of injec-

tion sites employed. All other organs examined presented a normal appearance except for a slight cloudy swelling. No significant variation in the findings between the rats on either of the specified diets was observed.

The liver damage produced by these injections of tannic acid solution was characterized by: ne-

DISCUSSION

The patients in the cases presented above died largely or solely as the result of a central liver necrosis. Such a necrosis has been observed, in our own cases and in those reported by others, only when the patient has been treated with tannic acid.

The sequence of possible lethal factors in burns treated with tannic acid is shown in Figure 2.

Other workers have burned experimental animals,<sup>8</sup> treated them with tannic acid jelly and produced a central liver necrosis comparable to that observed at autopsy in human beings who had

been treated with tannic acid. In our experiments, a series of rats was subcutaneously injected with chemically pure tannic acid and a central liver necrosis, comparable to that seen in the human patients, was produced. In these experiments, the degree of liver damage was in direct proportion to the amount of tannic acid injected subcutaneously. Similar results have been obtained after in-

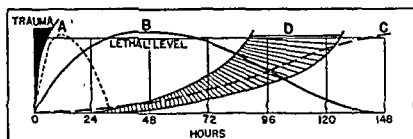


FIGURE 2. Sequence of Lethal Factors in Burns Treated with Tannic Acid (Adapted from Gunn and Hillsman<sup>1</sup>).

- A. Reflex shock from fright and pain.
- B. Secondary shock or peripheral vascular failure due to increased capillary permeability and fluid loss or shift.
- C. Bacterial contamination, which may become active infection in thirty-six to forty-eight hours.
- D. Tannic acid poisoning, clinically demonstrable after thirty-six hours and fatal, owing to specific hepatitis, in ninety hours or more; the shift from vertical to horizontal crosshatching indicates the trend of increasing liver damage.

jection of rabbits and guinea pigs with tannic acid. No factor other than tannic acid has entered into the production of liver damage in these experiments.

### CONCLUSIONS

In patients with severe burns treated with a tannic acid solution, tannic acid jelly or tannic acid and silver nitrate solutions, tannic acid poisoning resulting in a hepatitis may become clinically and chemically demonstrable within thirty-six hours and may result in death from a specific central necrosis of the liver in from eighty to one hundred and thirty hours or more.

The specific central necrosis of the liver due to tannic acid poisoning should be distinguished from the cause or causes of the so-called "toxemias" of burns and scalds.

### REFERENCES

1. Gunn, J., and Hillsman, J. A. Thermal burns. *Ann. Surg.* 102:429-443, 1935.
2. Harkins, J. N. Recent advances in the study of burns. *Surgery* 3:430-465, 1938.
3. Wells, D. B. The aseptic tannic acid treatment of diffuse superficial burns. *J. A. M. A.* 101:1136-1138, 1933.
4. Pack, G. T. The pathology of burns. *Arch. Path. & Lab. Med.* 1:767-785, 1926.
5. Wilson, W. C., Macgregor, A. R., and Stewart, G. P. The clinical course and pathology of burns and scalds under modern methods of treatment. *Brit. J. Surg.* 25:826-855, 1933.
6. Belt, T. H. Liver necrosis following burns, simulating the lesions of yellow fever. *Jour. Path. & Bact.* 48:493-498, 1939.
7. McClure, R. D. The treatment of the patient with severe burns. *J. A. M. A.* 113:1808-1812, 1939.
8. Buss, L. J., and Hartman, F. W. Histopathology of the liver following superficial burns. *Am. J. Clin. Path.* 11:275-287, 1941.

### DISCUSSION

DR. W. IRVING CLARK (Worcester, Massachusetts): I doubt if many of us here have followed the effect of tannic acid treatment in cases of fatal burns through to the conclusion of examination of the liver.

To me, the whole matter is extremely new, and I probably have not been following the literature, although I believe, from talking to Dr. Wells, that the literature is not very profuse on this subject.

It is interesting to follow the exact course of argument in this paper. In the first place, the statement is made definitely that there has been no pathological examination showing necrosis of the liver in cases of burns prior to the use of tannic acid; secondly, this is corroborated by finding necrosis of the liver in the cases presented; thirdly, animal experimentation has been carried out in which animals have been burned, subjected to tannic acid treatment and, then, autopsied, with the finding of central liver necrosis; and fourthly, animal experimentation by tannic acid alone has presented liver necrosis.

The cause of this necrosis is unknown. There has been much discussion about toxemia, which has generally been accepted by most authors. One finds in the literature that the toxemia of burns is a recognized condition, but whether it is due to histamine or to some other substance has never been definitely proved.

The interesting points that I should like to bring out are that chloroform produces a somewhat similar picture, and that inhalation of the fumes of chlorinated hydrocarbons causes a very similar necrosis.

In each of these cases, chloroform and the chlorinated hydrocarbons, one finds that the greater the amount of chlorine in the formula, the more definite and more acute the necrosis. For example, with carbon tetrachloride, a long exposure and a considerable amount of fume must be present before necrosis occurs, whereas with the more complicated chlorinated hydrocarbons such as the "pentas" and "hexas," the condition occurs with comparatively slight exposure.

Those two drugs may perhaps give a suggestion of the cause of this central necrosis. It does not seem logical that tannic acid itself should produce it; possibly, it does, but the question is whether the tannic acid may not produce in the body a change in the metabolism in some way by which there is hyperchlorination of the tissues. I think that this is a purely speculative matter, which should be discussed by pathologists in the future; this may be a step toward the solution of the problem.

The question that I suppose we are all asking ourselves is this, Do these experiments suggest that tannic acid as a treatment of burns should be omitted and some other form of treatment employed?

DR. WELLS (closing): The question that one immediately asks is, If tannic acid produces a specific and often fatal hepatitis, should it be abandoned as a local dressing in severe diffuse burns?

The employment of tannic acid is still, in my opinion, the best treatment for the local injury, and I am not quite ready to abandon it. It may result in the death of certain patients who have been burned, but, frankly, I know of no better local dressing at the present time. Operations for cancer of the stomach may result in the death of certain patients, since the mortality from the operation of subtotal or total gastrectomy is not negligible. However, gastric resection is at present the best treatment for carcinoma of the stomach, and in the hope of saving a patient doomed to die unless the growth can be totally extirpated, both patient and surgeon must accept the risk. A consideration of the mortality in more than 700 burns

treated at the Hartford Hospital during the last twenty-five years shows that since tannic acid was introduced the gross mortality has been cut in half. This is not by any means entirely due to the employment of tannic acid —

I am sure of that. Many factors have entered into the improvement of the records, but I am satisfied that tannic acid has helped to reduce the morbidity and mortality of burns.

## PRESIDENTIAL ADDRESS\*

JAMES B. WOODMAN, M.D.†

FRANKLIN, NEW HAMPSHIRE

MY father, who was a physician in a small town in central New Hampshire, once told me that, when the way seemed dark and I might be blamed for what was not my fault, I should remember that there would also be times when I would be praised and honored more than I deserved.

The latter part of this admonition comes to my mind in the present situation. And I consequently wish to express my heartfelt appreciation for the high honor of being the president of this society, and to tell you that I have for the past year been inwardly basking in the warming sunshine of your favor.

This evening, it seems not inappropriate to present to you briefly four of the names that have made New Hampshire medical history, and the history of the Dartmouth Medical School, noteworthy.

In presenting Drs. Twitchell, Mussey, Crosby and Peaslee, may I remind you that the whole state of New Hampshire contains fewer souls than the city of Boston alone, and that in the period of which I speak we were largely a farming population, widely scattered, with no hospitals and no centers, in the modern sense, for medical research? There were no modern laboratories, no electricity, no trains, no automobiles, no telephones, no good roads and, worst of all, no asepsis and, until near the end of the period, no anesthetics. Can you not see these gentlemen starting out for a distant village or farm, in their clothes of a former generation, on horseback, or in their two-wheeled chaises, toiling over the sandy, snow-bound or muddy roads? And before them and after them, one generation after another, struggling toward the light.

These four great men and great surgeons, country doctors and pioneers of their line, were all New Hampshire men. They were educated at Dartmouth College. They worked and taught at the Dartmouth Medical School. They passed on the knowledge they acquired to future gen-

erations. They were all a part of the New Hampshire medical tradition of which we are so proud.

Amos Twitchell was born in Dublin on April 11, 1781, on the slopes of old Mt. Monadnock, and it was said of him that he was as grand and honest as the old mountain itself. He possessed initiative, and was of the type of pioneer surgeons who have done so much the world over to make our present-day work possible. He was a poor farm boy, entirely lacking in this world's goods but blessed with an ambition that is a greater endowment. He prepared for college at New Ipswich Academy, entered Dartmouth at the age of seventeen, received his degree in 1802, and immediately began the study of medicine under Dr. Nathan Smith. He became a very proficient anatomist and in due time became assistant to Dr. Smith and was thus associated with him for some time at the medical school. He then practiced for short periods in Norwich, Vermont, and Marlboro, New Hampshire.

While in Marlboro, he encountered the case that brought him prominence at the time, and fame ever since. In October, 1807, John Taggart, of Sharon, had been shot in the neck while attending some military maneuvers. His jaw was shattered, all adjacent parts were severely bruised, and extensive mortification had set in. On the tenth day, while dressing the wound, Dr. Twitchell remarked that the common carotid artery was bare and appeared to be sloughed on its surface. While he was leaving the house, a terrific hemorrhage started, the blood spurting, as he says in his account of the case, a distance of three or four feet. He swiftly removed the dressings and placed his thumb over the bleeding point, and with only the help of the boy's mother, he cut down on the artery and finally succeeded in working around it by blunt dissection and getting a ligature on it. This was followed by some oozing, and as soon as pressure was removed, by some spurting. The lad was by this time unconscious and his condition was precarious, so that no further attempt at ligation was attempted. The bleeding point was then compressed by a small piece of dry sponge,

\*Presented at the annual meeting of the New England Surgical Society, Hanover, New Hampshire, September 5, 1941.

†Member of staff, Franklin Hospital, Franklin, New Hampshire.

covered by larger pieces to a depth of two or three inches, and this inverted cone was held down by bandages about the head and neck for pressure. The patient recovered. This operation was original, so far as Dr Twitchell was concerned although it had been performed by Fleming, an English surgeon, in 1803, it was not reported until 1817.

Dr Twitchell did all the major operations of the day, and did them repeatedly. In one year, he performed three tracheotomies for the removal of foreign bodies, and all were successful. Can you visualize him doing this emergency operation on a small infant's short, fat neck and without an anesthetic? He frequently operated for stone in the bladder. In 1838, he removed the arm, scapula and part of the clavicle for an enormous osteoma; this was the third time such an operation had been done, each previous one having been performed by a New Hampshire surgeon. He trephined the tibia for abscess, did excisions of the joints and had performed ovariectomies before it was known that McDowell had done the operation.

Dr Twitchell was a fine Christian, a genial gentleman and a tireless worker; he was extremely temperate and inclined to be a vegetarian. He was three times president of the New Hampshire Medical Society and always took an active part in the meetings, giving much attention to the eradication of quacks and charlatans, with which the state seemed to be afflicted at this time.

He was offered professorships at Dartmouth Medical School, Castleton and Vermont University but was unable to accept, partly from financial considerations and partly on account of his health. In his correspondence, I find a letter to the president of Dartmouth College in which he expressed the hope that the stipend might be raised to \$1200 per annum, that he might not be obliged to sustain too great a financial loss.

Reuben Dimond Mussey was born in Pelham on June 23, 1780. He was the son of Dr John Mussey, who bore a good reputation as a physician in his locality. There was not much money available in the family, but after district school he managed to attend the academy at Amherst. He was then obliged to earn enough for his further education by working on a farm and teaching school. His father had been able to teach him Latin, which was a prerequisite in those days. He must have worked to good advantage, for at the age of twenty-one he entered the junior class at Dartmouth College. He continued to teach during vacations, and he graduated from college in 1803 and immediately became a pupil of Dr Nathan Smith. At the end of this course, he sustained a public examination, and read and de-

fended a thesis on dysentery; the degree of B.M. was conferred on him in 1805. In 1812, he received his M.D. from the University of Pennsylvania School of Medicine. He was then called back to Hanover, where he was a professor in the medical college from 1814 to 1838. He then taught at Bowdoin for four years, later, he was professor of surgery at the University of Cincinnati College of Medicine for fourteen years and at Miami Medical College, which he founded, for five years.

As a surgeon, he enjoyed a reputation second to none in the state.

So-called brilliant surgery he regarded with contempt. He cared not to make a figure but to benefit his patient, not to gain eclat, but to save human life. He believed much in skilled surgery, something in nature, but most of all in God. Frequently on the eve of a great operation he knelt at the bedside and sought skill and strength and success from the great source of all vitality.

Doubtless, the confidence and sense of peace following this must have been of great advantage to both surgeon and patient at the operation. I think you will all agree with me that we have a dread of operating on one who lacks this confidence.

Mussey's famous discussion with Sir Astley Cooper over the healing of intracapsular fractures is well known and gave him, at the time, much prominence, since it was somewhat unusual, as he remarked, to win an argument with "one who was always positive, and sometimes right."

Dr Mussey is said to have been very skillful with his hands and to have handled the knife precisely and cleanly, a quality conducive to good healing in his day as in ours. Evidence of his dexterity is a clock still in the possession of his descendants; he made this when a young man. While in college, he also made his own shoes.

The case that brought him the greatest fame was probably that in which he successfully ligated both carotid arteries. He did this operation for Mr Jason Pettee, a resident of Hanover, and the operation was performed for a bleeding nevus of the vertex of the head, which threatened a speedy death. He tied one carotid, and twelve days later he tied the other. A few weeks later, he successfully removed the tumor. This was the first recorded case in which both carotids were successfully tied. Naturally enough, the operation gave him a reputation all over the surgical world.

He removed a boy's tongue, which measured eight inches in circumference and projected five inches beyond the jaws, and the patient recovered. At one operation, he removed the scapula and a large part of the clavicle from a patient for whom he had previously amputated at the shoulder joint. Dr Mussey mistakenly supposed that this



was the first operation of the kind in the history of surgery. As a matter of fact, it was first done by Dr. Dixi Crosby in 1836, and then by Dr. Mussey in 1837 and by Dr. Twitchell in 1838—all New Hampshire surgeons. Dr. Mussey several times removed the upper and portions of the lower jaw. His records show that he did lithotomies in 49 cases; all but 4 patients recovered. He repaired strangulated hernias in 40 cases, with only 8 deaths. He treated 45 cases of varicocele successfully. He operated for perineal fistula in 4 cases and for impermeable stricture of the urethra in 2, and did a large number of plastic operations, with fine results. He also successfully treated a rectovaginal fistula. These are only a few samples of the enormous amount of work he was constantly carrying on.

Dr. Mussey was a small man with a high forehead, high cheek bones, a thin face and square chin. He had a brusque, rather forbidding manner. His Puritan ancestry gave him none of the sparkle that we now speak of as personality. He won his reputation purely on merit. His motto was, "Do well and wait." As a young man, he was dyspeptic and developed the habit of living on a strictly vegetable diet, and this rule was followed more or less all his life. He was a very religious man and very abstemious. Many of his speeches and pamphlets were directed against the use of alcohol and tobacco. At one time during his later life, his physician prescribed some stimulant. He finally consented to take some brandy in eight-drop doses, from which he said he could feel quite a strong effect. In those days, when liquor was so universally and so freely used, he must have felt that he had won his argument for temperance, for in spite of his dyspepsia he lived to the ripe age of eighty-six.

Dr. Mussey's sons, grandsons, great-grandsons and so on, without a break in the line, were physicians down to the seventh generation, which is represented, I am informed, at the present time by a young man who is a student at Dartmouth Medical School.

Dixi Crosby was born at Sandwich on February 9, 1800, shortly after his father, Dr. Asa Crosby, had been ordered out of Moultonboro by the sheriff for fear that he might become a financial burden on the town, on account of his poor health. Dr. Asa had ten sons, several of whom became physicians. Prior to Dixi's birth, there naturally had been much speculation about whether this child, too, would be a boy. Dr. Asa had favored another son, and when the youngster arrived on the scene and it was ascertained that it was a boy, the exulting father exclaimed "*Dixi*," or "I told you so." And Dixi he remained.

Up to his nineteenth year, young Crosby had not been much interested in books and had made an early venture into business. This however, was not a success, and he finally returned home to Gilmanton, where the family then resided. He studied with his father, a method of gaining knowledge and experience prevalent in those days, and one that, it seems to me, has much to recommend it. He also attended Gilmanton Academy and later went to Dartmouth College. He was a keen student of anatomy, and one of his biographers has a good deal to say regarding certain difficulties in which he found himself over the procuring of anatomic material, which at that time was extremely difficult to obtain.

After receiving his degree from Dartmouth Medical School, he practiced for ten years in Gilmanton and for three years in Laconia, then known as Meredith Bridge. He had by that time established a fine reputation as a surgeon, and in 1838 he was called to take the chair of surgery and obstetrics at Dartmouth by Dr. Mussey, who was retiring. He held this position for thirty-two years.

His brother, Nathan, in his book, *A Crosby Family*, tells of Dixi's first major operation. It was done while Dixi was in his first year of medical study. He accompanied his father to a consultation in the case of a man whose leg had been frozen, and whose condition was most critical. It was agreed by the physicians that amputation at an earlier stage might have saved the patient's life, but that it was now too late to attempt it. Young Crosby urged that the operation still be performed. The elders shook their heads. He even proposed to attempt it himself, but this was met with a storm of disapproval. During the night, the patient was being attended by young Crosby, and the following conversation is quoted. "Look here, young man, did you ever cut off a leg?" "No sir, but I should like to." "Will you cut off mine?" "Yes, if you will let me." "Well, young man, if I live till morning you shall cut off my leg, and I will take the chances." In the morning, all the elders joined in protest against the operation, and Dixi's father said, "Don't do it, Dixi, you can't succeed and if the man dies they will kill you." But the patient was firm, and the student was ready. The leg was removed, and the man recovered.

During the following year, father and son were called in while at a distant village to see a man who had just had a severe accident to his leg, demanding amputation. The father was for giving it up, since he did not have his instruments with him. The more resourceful young Crosby sharpened a carving knife, filed a saw and did the amputation, which was successful.

These early incidents are pointers to his later teachings to his pupils. He often said to them,

"Depend on yourselves, young gentlemen, take no man's diagnosis, but see with your own eyes, feel with your own fingers, judge with your own judgment and be the disciple of no man"

Dr Crosby, although a surgeon by nature and by preference, was in no modern sense, a specialist. His professional and professorial labors included obstetrics as well as surgery, and his practice was enormous. Probably no man ever did more surgery in the State than he, and his surgical diocese extended from Lake Champlain to Boston.

Dr Crosby was the first to devise the method of reduction of dislocations of the phalanges by flexion, some of which had previously been irreducible. He was the first to open abscess of the hip joint. Most of his operations were done before he had ever seen them done by anyone. He was not a rapid or spectacular operator. His motto was that an operation was soon enough done when it was well enough done.

His brother speaks of him as follows:

[He was] a handsome, brilliant, cheery, chatty man. He could sing, tell a good story, was kindly and civil, had agreeable manners, had cultivated the proprieties of social life, and had entered upon a religious life, a combination forming ballast to stand any amount of sail or storm, any success or discouragement.

Dr Crosby passed his declining years in Hanover and passed on his mantle to his distinguished son and inseparable companion, Dr Alpheus Benjamin Crosby, affectionately known as "Dr Ben."

Edmund Randolph Peaslee was born in Newton on January 22, 1814. He was educated at New Hampton and Atkinson academies and at Dartmouth College and Dartmouth Medical School from which institution he graduated in 1838. He also received his M.D. degree from Yale. Following this, he studied extensively in Europe. He was then recalled to Dartmouth and appointed lecturer in anatomy and physiology. He taught at Dartmouth for twenty-seven years. He also taught at Bowdoin, at New York University College of Medicine and at Bellevue. He received an LL.D. from Yale University, as well as Dartmouth. He was a great scholar and a great gentleman. His greatest work was done in the field of gynecology, and his writings on gynecologic subjects were profound and scholarly. He was the first to remove both ovaries through a single incision. He was also the first to use vaginal drainage after a laparotomy. He was the first to flush out the abdominal cavity after laparotomy.

One of his friends described him as a tall, spare man, with a long beard, which early became snow white. In appearance, he was said to be as fragile

and as cold as an icicle from his own native land Oliver Wendell Holmes, who was his contemporary on the faculty of Dartmouth Medical School, said, "He looked as if his circulating capital might consist of a hundred or two red globules, with twice as many white ones, in a half a pint of serum, yet he outlived scores of prize-fighters." His appearance must have been deceptive, for he did an enormous amount of work for many years and was ever ready for more.

He was a most sympathetic and helpful friend and adviser of his students, all of whom he regarded and spoke of as "my boys."

He, too, was a fine Christian gentleman, with whom duty was the ruling passion. His contemporaries expressed their esteem for his character and scholarly attainments by making him president of the New Hampshire Medical Society, of the New York Academy of Medicine, of the Medical Society of the County of New York, of the New York Obstetrical Society, of the New York Pathological Society and of the American Gynecological Society; at the time of his death, he was a trustee of Dartmouth College and of the New York Academy of Medicine, corresponding fellow of the Obstetrical Society of Berlin and honorary fellow of the obstetrical societies of London, Boston and Louisville.

\* \* \*

These, in brief, are the lives of four great seekers for the light. Their careers suggest to me that oft-quoted passage:

Happy is the man that findeth wisdom, and the man that getteth understanding. For the merchandise of it is better than the merchandise of silver, and the gain thereof than fine gold. She is more precious than rubies, and all the things thou canst desire are not to be compared unto her. Length of days is in her right hand, and in her left hand riches and honour. Her ways are ways of pleasantness, and all her paths are peace.

Proverbs 3 13-17

336 Central Street

#### BIBLIOGRAPHY

- Blaissell, F. *One Hundred Years of New Hampshire Surgery. A brief sketch of the life and work of New Hampshire surgeons from 1700 to 1900.* (Read before the New Hampshire Surgical Club at Plymouth, N. H., September 18, 1907.) 40 pp. Manchester, N. H.: J. B. Clarke Co., 1907.
- Bowditch, H. I. *Memoir of Anson Tuntitch.* 5212 pp. Boston: J. Wilson and Son, 1851.
- Crosby, A. B. *An Address Commemorative of Reuben Dimond Missey.* 24 pp. Manchester, N. H.: J. B. Clarke Co., 1879.
- Crosby, N. *A Crosby Family.* Josiah Crosby, Sarah Fish and their descendants by their grandson Nathan Crosby. 143 pp. Lowell: Mass. Stone, Huse & Co., 1877.
- Hanks, H. T. *Memoir of Edmund Randolph Peaslee, M.D., LL.D.* 14 pp. Read before the New Hampshire Medical Society at its annual convention held in Concord, June 18 and 19, 1888.
- Lord, J. K. *A History of the Town of Hanover, New Hampshire.* 339 pp. Hanover, N. H.: Dartmouth Press, 1978.
- Luce, T. W. *Personal remarks of the retiring president.* *Transactions of the New Hampshire Medical Society.* Concord, May 25 '96. 176 pp. 7074.
- Mussey, R. D. *What Shall I Drink?* 35 pp. Boston: American Tract Society.
- Richardson, L. B. *History of Dartmouth College.* 2 vol. Hanover, N. H.: Dartmouth College Publications, 1937.

## CLINICAL ASPECTS OF PAROXYSMAL RAPID HEART ACTION\*

LOUIS WOLFF, M.D.†

BOSTON

**N**UMEROUS publications bearing on the occurrence, mechanism and treatment of the various paroxysmal tachycardias are available. Analysis of the clinical manifestations of paroxysmal rapid heart action has not, however, received the attention it deserves. These data are essential to a complete understanding of the clinical problems created by these arrhythmias under different circumstances, of their prognosis and, to some extent, of their treatment. This study was made in an attempt to provide such data.

## MATERIAL

Data were obtained in 125 cases. Electrocardiograms were made during the paroxysm in every case but 1, and during normal rhythm in most. Ventricular rates were obtained from the electrocardiograms. There were 81 cases (65 per cent) of paroxysmal auricular fibrillation, 24 (20 per cent) of paroxysmal auricular tachycardia, 11 (8 per cent) of paroxysmal auricular flutter and 9 (7 per cent) of paroxysmal ventricular tachycardia. The types of heart disease‡ represented were: valvular heart disease (including 2 cases of subacute bacterial endocarditis), 25 cases (18 per cent) — 16 of these patients had mitral stenosis, 5 had aortic valvular disease without other valvular involvement, and 4 had mitral stenosis and aortic valvular disease (in 1 case, combined with tricuspid stenosis); angina pectoris of effort, 20 cases (14 per cent); acute or recent cardiac infarction, 24 cases (17 per cent); chronic arterial hypertension, with or without definite evidence of heart involvement (cases with concomitant valvular or coronary-artery disease are not included in this group), 23 cases (17 per cent); coronary-artery disease without angina of effort or acute or recent cardiac infarction, 10 cases (7 per cent) — the term "asymptomatic coronary disease" was applied to this group; hyperthyroidism, 8 cases (6 per cent); normal hearts, including 4 cases of hyperthyroidism, 25 cases (18 per cent); miscellaneous types, comprising 1 case each of acute simple fibrinous pericarditis, chronic cor pulmonale and acute cor pulmonale, 3 cases (2 per cent). Among

these cases, there were 19 patients with congestive failure and 2 with cardiac asthma.

The type of patient, ventricular rate, cardiac lesion, functional status of the circulation and the occurrence of palpitation, pulmonary congestion, angina pectoris (or status anginosus), circulatory collapse, congestive failure, various cerebral phenomena and embolism were analyzed, to determine what correlations existed. The available data in some cases were inadequate for clinical analysis; these cases, in addition to the others, were utilized to determine the influence of digitalis on the ventricular rate in paroxysmal auricular fibrillation.

## ASYMPTOMATIC CASES

Symptoms were not provoked by paroxysms of rapid heart action in 41 cases, almost one third of the entire series. The ages of the patients ranged from two to eighty years. This group included 5 cases (12 per cent) of paroxysmal auricular tachycardia, 28 (68 per cent) of paroxysmal auricular fibrillation, 5 (12 per cent) of paroxysmal auricular flutter and 3 (7 per cent) of paroxysmal ventricular tachycardia. The incidence of the various arrhythmias in this group is no different from that of the entire series.

Thirteen patients (32 per cent) had normal hearts, including 3 with hyperthyroidism (7 per cent); 10 (24 per cent) had hypertension with or without definite evidence of heart involvement (1 of these had hyperthyroidism); 10 (24 per cent) had acute or recent cardiac infarction; 4 (10 per cent) had asymptomatic coronary-artery disease; 2 (5 per cent) had rheumatic heart disease, and 1 had acute fibrinous pericarditis, 1 chronic cor pulmonale, 1 acute cor pulmonale and 1 angina pectoris. There was 1 case of congestive failure. The incidence of thyrotoxicosis, hypertension, acute or recent myocardial infarction and asymptomatic coronary disease is the same in this group as in the entire series of 125 cases, whereas the incidence of normal hearts is higher, and that of valvular disease, angina pectoris and congestive failure much lower than in the series as a whole. Embolism occurred in 4 cases. Extracardiac factors, which may possibly have had some bearing on the occurrence of the arrhythmia, were present in each case with a normal heart§: namely, anesthesia and

\*From the Cardiac Clinic, Beth Israel Hospital.

†Instructor, Courses for Graduates, Harvard Medical School; associate visiting physician, Beth Israel Hospital.

‡Classified according to etiology, the 125 cases accounted for 138 listings, this discrepancy being occasioned by the inclusion of some cases of coronary-artery disease in three different groups — asymptomatic, angina of effort and acute cardiac infarction — when observations were available during paroxysms of rapid heart action in more than one of these clinical states.

§There are, of course, many examples of paroxysmal rapid heart action in patients with normal hearts in whom obvious or apparent exciting causes are not evident.

surgery, hyperthyroidism, acute mediastinitis, bronchopneumonia, gangrenous appendicitis and subacute yellow atrophy of the liver.

The ventricular rates ranged from 80 to 250, but were 150 or less in 18 (44 per cent) and more than 170 in 8 (19 per cent) of the cases. Of the 18 patients with rates of 150 or less, the paroxysm of rapid heart action occurred postoperatively in 3, following hemiplegia in 1, and during the course of bronchopneumonia in 2. On the other hand, of the remaining 23 cases with rates exceeding 150, 9 were postoperative; 1 patient had subacute bacterial endocarditis, 1 had gangrenous appendicitis, 1 had acute rheumatic fever, and 1 had bronchopneumonia. Seven of the 8 cases in which the rate exceeded 170 were postoperative. Only 11 cases were not postoperative or did not have extracardiac disease, and in 10 of these the ventricular rate was less than 170; none of these patients had normal hearts. In 3 of the cases with embolism, the ventricular rate was 140 or less.

#### CASES WITH PALPITATION

Palpitation was the sole symptom provoked by paroxysmal rapid heart action in 17 cases. The ages of the patients ranged from twenty-one to sixty-one years. Of these, there were 3 cases (18 per cent) of paroxysmal auricular tachycardia, 13 (76 per cent) of paroxysmal auricular fibrillation, and 1 (6 per cent) of paroxysmal auricular flutter. The incidence of the various arrhythmias in this group differs from that of the entire series of 125 cases only in the absence of ventricular tachycardia. Eight patients (47 per cent) had normal hearts, 4 (24 per cent) had hypertension, 4 (24 per cent) had rheumatic heart disease, and 2 (12 per cent) had angina pectoris—1 with rheumatic heart disease. The occurrence of hypertension, rheumatic heart disease and angina pectoris was the same in this group as in the entire series of 125 cases, whereas the incidence of acute or recent myocardial infarction was much less and, in normal hearts, much greater than in the entire series. There was no case of congestive failure or embolism.

The ventricular rate was 150 per minute, or less, in 11 (65 per cent) of the cases, and more than 170 in only 1 case. In contrast to the group without symptoms, there were no postoperative cases, and the only extracardiac conditions were a lung tumor and carbon monoxide poisoning. Moreover, 4 patients were described as "nervous," and 1 was having menopausal symptoms. Of the 8 patients with normal hearts, 3 were nervous, 1 had a lung tumor, and 1 had carbon monoxide poisoning. The ventricular rates in the 2 cases of angina pectoris were 124 and 140, respectively, and

in the 4 cases of rheumatic heart disease 124, 160 to 180; 140, and 110 to 130, respectively.

#### CASES WITH PULMONARY CONGESTION

Dyspnea, wheezing, pulmonary edema and hemoptysis may be provoked by paroxysmal rapid heart action. After exclusion of cases of congestive failure and angina pectoris, there remain 11 in which one or more of these symptoms were observed during paroxysms of rapid heart action.

Mitral stenosis was present in 10 cases, and hyperthyroidism in 1. The paroxysm of rapid heart action in the latter occurred during an acute illness characterized by fever, marked but temporary dilatation of the heart and pericardial and pleural friction rubs; following subsidence of the acute condition and control of the hyperthyroidism by thyroidectomy, numerous paroxysms of auricular fibrillation, during a period of eleven years, failed to provoke dyspnea. There were 9 cases of auricular fibrillation, and 2 of auricular flutter. The slowest ventricular rate, 140 per minute, was observed in 2 cases, whereas in the rest, the rate was 150 or more. Embolism complicated the arrhythmia in 4 cases. The ages ranged from nineteen to fifty-five years.

However, not all patients with mitral stenosis exhibit manifestations of pulmonary congestion during paroxysms of rapid heart action. It was not present in 4 cases. In 3, the ventricular rates were 124, 140, and 110 to 130, respectively, and in only 1 was the rate greater than 150 (160 to 180).

#### CASES OF ANGINA AND CORONARY-ARTERY DISEASE

Angina pectoris was induced by paroxysmal rapid heart action in 15 cases. The ages in this group ranged from forty-four to seventy-five years. There were 4 cases (27 per cent) of paroxysmal auricular tachycardia, 10 (67 per cent) of paroxysmal auricular fibrillation, and 1 (6 per cent) of paroxysmal ventricular tachycardia. It is clear that the incidence of the various arrhythmias in this group is not significantly different from that in the entire series of 125 cases. The ventricular rate was 150 per minute or more in 12 cases, 140 in 2, and 120 in 1. Embolism complicated the arrhythmia in 2 patients with paroxysmal auricular fibrillation. There were 2 cases of mitral stenosis, with evidence of coronary-artery disease in 1, and 1 case of hyperthyroidism in which a routine post-mortem examination showed normal coronary arteries. Hypertension was present in 5 cases. Twelve patients gave a clear history of angina on effort, but no such history was obtained in 3 cases. In one case, paroxysms of auricular tachycardia recurred for thirty-six years without induc-

ing anginal pain; finally, however, although angina of effort had never yet been experienced, a paroxysm provoked pain. A short time after this episode, cardiac infarction occurred, and following recovery from the acute condition, angina was induced both by effort and by paroxysmal rapid heart action. Another case was similar, in that angina was induced by paroxysms of rapid heart action, but not by effort; it differed in one important aspect, however: cardiac infarction did not supervene, despite the lapse of considerable time. This patient was elderly and crippled by arthritis. The first attack of paroxysmal auricular fibrillation in still another case provoked angina pectoris, which had never been produced by effort. However, shortly following this event, there was an attack of cardiac infarction, uncomplicated by any disturbance of the heart rhythm. During convalescence, a paroxysm of auricular fibrillation failed to produce any symptoms but palpitation. In none of these cases was the variation in response to paroxysmal rapid heart action ascribable to a change in the ventricular rate.

In contrast to these 15 cases are 3 in which paroxysmal rapid heart action failed to induce angina pectoris, although effort did provoke this syndrome. The ventricular rates were 124, 140 to 145, and 140 per minute, respectively.

In 8 cases with significant coronary-artery disease but without a history of angina on effort or acute or recent cardiac infarction, it is noteworthy that paroxysmal rapid heart action did not induce angina pectoris. In 6 cases, the ventricular rates were quite rapid, being 215, 175, 166, 190, 200 and 150 per minute, respectively. Significant coronary-artery disease was revealed by post-mortem examination in 4 cases, and by a history of old cardiac infarction antedating the occurrence of paroxysmal ventricular tachycardia in the other 2. The 2 remaining cases of asymptomatic coronary-artery disease had ventricular rates of 120, and 120 to 140, respectively.

Twenty-four cases of acute and recent cardiac infarction were complicated by paroxysmal rapid heart action—3 (13 per cent) by paroxysmal auricular tachycardia, 13 (54 per cent) by paroxysmal auricular fibrillation, 4 (17 per cent) by paroxysmal auricular flutter, and 4 (17 per cent) by paroxysmal ventricular tachycardia. The incidence of auricular flutter and ventricular tachycardia was higher than in the entire series of 125 cases, but otherwise there was no difference between this group and the entire series. The occurrence of paroxysmal tachycardia is unusual before the third day following the onset of cardiac infarction, the greatest incidence coming on or after the fifth day. Thus, of 18 cases studied ade-

quately, 14 exhibited paroxysmal rapid heart action three days to two months following acute cardiac infarction; in no case was anginal pain induced, even though the ventricular rate was 150 per minute, or more, in all but 3. None of these patients experienced anginal pain spontaneously or as the result of effort. In 1 case, angina of effort continued after an episode of myocardial infarction and was also induced by paroxysmal ventricular tachycardia at a rate of 187. In 3 cases, paroxysmal rapid heart action and cardiac infarction appeared to have a simultaneous onset. In 1 case, paroxysmal auricular tachycardia and cardiac infarction occurred simultaneously, and, as so often happens under these circumstances, the precise sequence of events remains uncertain; the significant fact is the continuance of the paroxysmal tachycardia for twenty-four hours following the cessation of pain. Four and a half hours after a similar onset in another case, the paroxysmal tachycardia ended, but pain and shock continued for three or four days. Prior to the onset of the attack in these 2 cases, angina on effort had never been experienced, and four years prior to the attack in the latter case, paroxysmal auricular tachycardia with a rate of 200 failed to induce angina pectoris. The third case was similar to these in that paroxysmal auricular fibrillation apparently induced angina pectoris in a patient who had never experienced such pain on effort, and the obvious fact soon emerged that cardiac infarction was in progress. The possibility that paroxysmal rapid heart action precipitated acute coronary thrombosis or cardiac infarction in these 3 cases must be considered. It has been suggested<sup>1</sup> that paroxysmal rapid heart action, by further impairing an already abnormal coronary circulation, may predispose to or precipitate acute coronary thrombosis or cardiac infarction; convincing evidence is difficult to obtain, but 2 cases in addition to those just described are suggestive. In these, pain occurred some hours after cessation of a paroxysmal arrhythmia; myocardial infarction was found at autopsy in both.

#### CASES OF CONGESTIVE FAILURE

Congestive failure was present in 19 cases, in 15 of which it was possible to estimate the effect of paroxysmal rapid heart action on the degree of failure. There were 6 cases (40 per cent) of paroxysmal auricular tachycardia, 5 (33 per cent) of paroxysmal auricular fibrillation, 2 (13 per cent) of paroxysmal auricular flutter, and 2 (13 per cent) of paroxysmal ventricular tachycardia. The ages ranged from thirty-four to sixty-eight years. Rheumatic valvular disease (including 1 case of sub-acute bacterial endocarditis) was present in 7 cases

(47 per cent), hypertension without additional etiologic factors in 4 (27 per cent), and coronary-artery disease in four (27 per cent). The ventricular rate was 150 per minute or more in 10 cases, 140 in 3, and 130 and 120, respectively, in 2. Embolism occurred in 1 case of paroxysmal auricular tachycardia and in 2 cases of paroxysmal auricular fibrillation, and in 1 case of mitral stenosis complicated by paroxysmal auricular flutter, autopsy revealed old splenic infarcts and terminal coronary thrombosis.

In 14 cases, there was noted, as a result of the paroxysms of rapid heart action, an increased severity of such manifestations as dyspnea, orthopnea, congested liver and edema, and a drop in the urinary output, or renal failure, coma and death, in some of these cases, there was a prompt and striking clinical improvement following the resumption of normal rhythm. Gross congestive failure was evident prior to the onset of tachycardia in all but 1 case, in which, however, chronic hypertension, cardiac enlargement and exertional dyspnea indicated the probability of incipient failure or poor cardiac reserve. Evidence of gross failure first appeared, and then rapidly progressed, at the end of ten days of paroxysmal auricular tachycardia with a ventricular rate of 210 per minute; rapid improvement followed resumption of normal rhythm. In an additional case, in which the ventricular rate was 120 per minute, the arrhythmia appeared to have no obvious influence on the functional status of the cardiovascular system.

#### CASES WITH CENTRAL-NERVOUS SYSTEM MANIFESTATIONS

Irrationality, confusion, psychosis, coma and convulsions may be observed during attacks of paroxysmal tachycardia. Six patients exhibited one or more of these manifestations. The ages ranged from sixty-one to seventy-one years. There were 2 cases of paroxysmal auricular tachycardia, 2 of paroxysmal auricular fibrillation, and 2 of paroxysmal ventricular tachycardia. Four patients had hypertension, and 2 had coronary-artery disease. There were 3 cases of congestive failure, 1 of cerebral embolism, 1 of pulmonary embolism, and 1 of pulmonary thrombosis. The ventricular rates were 150 to 200 per minute.

One patient was "euphoric and queer" before the onset of paroxysmal ventricular tachycardia, which precipitated an acute psychosis. In another, irrationality, which had been previously noted, was increased during a paroxysm of auricular tachycardia. Another patient showed signs of mental confusion accompanying an attack of auricular fibrillation, which was complicated by cerebral embolism. Paroxysmal auricular tachycardia in a

case of congestive failure brought about renal failure, which was followed by coma. Unconsciousness occurred as a transitory phenomenon at the onset of paroxysmal ventricular tachycardia in a patient with a ventricular rate of 190, whereas in another, unconsciousness and convulsions occurred at the end of a paroxysm of auricular fibrillation, presumably from cardiac standstill before the re-establishment of a normal sinus mechanism. In the last case, there were no heart sounds during the seizure, but unfortunately it was not possible to obtain an electrocardiogram during the period of apparent cardiac standstill.

#### CASES WITH VASCULAR COLLAPSE

Although a fall in blood pressure was commonly observed during paroxysmal rapid heart action, in only 15 cases did collapse occur. The ages ranged from thirteen to sixty-eight years. There were 5 cases (33 per cent) each of paroxysmal auricular tachycardia and paroxysmal auricular fibrillation, 3 (20 per cent) of paroxysmal auricular flutter, and 2 (14 per cent) of paroxysmal ventricular tachycardia. Four patients had normal hearts (1 with hyperthyroidism), 5 had mitral stenosis, 1 had free aortic insufficiency, 2 had angina pectoris, 2 had asymptomatic coronary artery disease, and 1 had recent cardiac infarction. Only 1 case of hypertension (in a patient with mitral stenosis) occurred in this group. Four patients had congestive failure. Embolism complicated the arrhythmia in 5 cases. The ventricular rate was 200 per minute or more in 7, or almost half the cases, and was less than 150 in only 2.

#### CASES OF EMBOLISM

Embolism complicated the paroxysmal arrhythmia in 18 cases; pulmonary-artery thrombosis occurred in 1 case. The ages ranged from nineteen to sixty-eight years. All types of arrhythmia were represented. 2 cases (11 per cent) of paroxysmal auricular tachycardia, 11 (58 per cent) of paroxysmal auricular fibrillation, 3 (16 per cent) of paroxysmal auricular flutter, and 3 (16 per cent) of paroxysmal ventricular tachycardia. Mitral stenosis was present in 7 cases, coronary artery disease in 7, hypertension in 4 (with mitral stenosis in 1), and a normal heart in 1. Four patients were in congestive failure. Pulmonary embolism occurred in 16 cases, but the diagnosis was doubtful in 2, cerebral, renal, splenic and axillary embolisms were also observed. The ventricular rates ranged from 120 to 220 per minute. Embolism preceded, and probably provoked, the arrhythmia in 3 cases, and was followed by vascular collapse in 7. Dyspnea occurred in only 5 cases, and hemoptysis in 2, all being cases of mitral stenosis;

pulmonary edema occurred in 1 case of mitral stenosis. In 2 cases, the advent of embolism appeared to provoke no symptoms; the ventricular rate was 120 and 140 respectively, in these.

#### EFFECT OF DIGITALIS

Digitalis was being taken by 29 patients prior to the onset of a paroxysm of auricular fibrillation in which observations could be made. The ventricular rates in these cases were compared with those in 52 patients who did not receive digitalis. The paroxysms observed numbered 30 and 55, respectively; the ventricular rate was less than 140 in 14 (47 per cent) and more than 140 in 16 (53 per cent) of the paroxysms in the former group, and less than 140 in 11 (20 per cent) and more than 140 in 44 (80 per cent) in the latter group. In 6 cases, observations of the ventricular rate were made in paroxysms of auricular fibrillation both before and after the administration of digitalis. The ventricular rate was significantly lower after digitalization in 4 of these and was unchanged in 2. The ventricular rate in 16 fully digitalized cases was less than 140 in 7, and 140 or more in 9; in 7 cases that were overdigitalized (excessive amounts of the drug, or digitalis intoxication), the ventricular rate was less than 140 in 4, and 140 or more in 3; in 2 partially digitalized cases, the rates were 140 and 130, respectively; in 4 cases, the amount of digitalis taken was unknown.

Among the 15 digitalized cases in which the ventricular rate was 140 or more, normal hearts were present in 4, acute cardiac infarction in 1, hyperthyroidism in 1, and congestive failure in 3; in the last 3 cases, the ventricular rates were the slowest of this group—140, 140 and 150, respectively. The group of 14 with ventricular rates under 140 contained no patients with normal hearts, 2 with hyperthyroidism (1 of whom received iodine in addition to digitalis), 2 with acute cardiac infarction, and 5 with congestive failure.

Digitalis administered between paroxysms of auricular fibrillation is effective in controlling the ventricular rate during the paroxysm in some, but not in all, cases. The ventricular rate was significantly slow in 20 per cent of patients who had not had any digitalis, a fact that should be considered in appraising the above data; moreover, in 2 cases in which digitalis appeared to be effective, other factors were operative—one patient, with hyperthyroidism, received iodine in addition to digitalis, and the other had a 2:1 auriculoventricular block. It is obvious that in more than half the patients digitalis did not prevent ventricular rates that were rapid enough to induce symptoms, even when excessive amounts of the drug were used. Digitalis is least effective in those with normal hearts, and displays its greatest influence on the

ventricular rate in patients with congestive heart failure.

Since it is not my purpose to provide an elaborate presentation of treatment, the consideration of the effect of digitalis and other therapeutic agents on the other arrhythmias is omitted.

#### DISCUSSION

Correlation of certain symptom groups with the ventricular rate, type of patient, cardiac lesion and presence or absence of embolism and congestive failure (Table 1) reveals that most of the symptoms are provoked under definite conditions and relations; and there is thus created, within broad limits, a fixed and uniform clinical pattern. The remaining symptoms, which are not susceptible to such correlation, must be differentiated from the cardinal manifestations of paroxysmal tachycardia and regarded as minor or noncharacteristic; some of these are nausea, vomiting, weakness, dizziness, precordial pain or aching, sweating, feeling of warmth, faintness, apprehension, nervousness, polyuria, fever and leukocytosis; a slight to moderate drop in blood pressure is very common, and rarely, in cases of congestive failure, the blood pressure may rise. Following a paroxysm of auricular tachycardia pain, tenderness and swelling of the left shoulder, accompanied by fever, leukocytosis and rapid sedimentation rate, were observed in 1 patient; these manifestations rapidly subsided.

The ventricular rate and, to a lesser extent, the type of arrhythmia are significant in determining symptoms. Symptoms are not often provoked by rates under 150 per minute, which may be regarded as the critical level, unless embolism complicates the paroxysm. With extremely rapid ventricular rates, on the other hand, symptoms are almost always induced, regardless of the type of heart lesion and even if the heart is normal. When symptoms fail to appear during paroxysms with rates somewhat above the critical level, the explanation is usually to be found in the type of patient, who is "insensitive" naturally or as the result of grave illness, or has been rendered so by heavy sedation. The group in which palpitation occurs as the only symptom differs most strikingly from the asymptomatic one in relation to the type of patient; "sensitiveness" is common, and conditions requiring heavy sedation are absent. The lack of symptoms other than palpitation is to be explained on the basis of the ventricular rate.

A comparison of the ventricular rates in the different types of rapid heart action is of some interest. The slowest rate (excluding cases of auricular fibrillation), 124, occurred in paroxysmal auricular tachycardia; the fastest rate, 260, in a case of auricular flutter with 1:1 ventricular response. The ventricular rate in auricular fibrillation is usually under 170, and only rarely 200 or more. The

fastest rates occur in auricular flutter during periods of 1:1 response. In paroxysmal auricular tachycardia, the ventricular rate, as a rule, does not exceed 220. Excessively rapid ventricular rates, in the vicinity of 300, were not observed in the present series, but many cases are on record. These are usually, probably always, examples of auricular flutter with 1:1 ventricular response.<sup>2-21</sup> Two cases of auricular flutter with 1:1 ventricular re-

gessive heart failure. The characteristic response in cases of compensated mitral stenosis consists of dyspnea, orthopnea, asthma, pulmonary edema and hemoptysis. These manifestations usually occur when the ventricular rate is 150 per minute or more; pulmonary congestion is not induced when the ventricular rate is well under this level, but is rarely absent when it is exceeded. These clinical phenomena, in some cases, may be less

TABLE 1. *Correlation of Clinical Data.*

SYMPTOM OR COMPLICATION	HEART LESION	VENTRICULAR RATE	TYPE OF PATIENT	EMBOLISM
Asymptomatic	None, or any type	Usually 150 per minute or less	'Insensitive'	Uncommon
Palpitation	None, or any type	Usually 150 per minute or less	'Sensitive'	Never
Pulmonary congestion	Mitral stenosis	Usually more 150 per minute or		Common
Angina pectoris	Angina pectoris of effort, occasionally, aortic valvular disease	Usually more 150 per minute or		Uncommon
Central nervous system manifestations				
Loss of consciousness, with or without convulsions	None, or any type	Usually 200 per minute or more (cardiac standstill) Rate unimportant		May occur (not essential) Always (cerebral)
Mental confusion or acute psychosis	None, or any type, hypertensive and coronary disease and congestive failure common	Rate unimportant if cerebral embolism occurs, otherwise usually 150 per minute or more	Functional nervous disorders or organic cerebral disease	May be causative (not essential)
Coma	Congestive failure, renal failure	Usually 150 per minute or more		May be causative (not essential)
Congestive failure	Any type (pre existing congestive failure or very poor reserve)	Usually more 150 per minute or		Common
Vascular collapse	None, or any type Aortic valvular disease None, or any type	Usually 200 per minute (less in elderly patients) Rate unimportant Rate unimportant		May occur (not essential) May occur (not essential) Always
Embolism	None, or any type (mitral stenosis commonest)		Commonest with auricular fibrillation, may occur with auricular flutter or paroxysmal tachycardia	

sponse occurred in this series, and may be added to those already reported.<sup>22, 23</sup>

The significance of the type of rhythm is seen in auricular fibrillation and paroxysmal ventricular tachycardia. Embolism is much more frequent in the former than in all the other types of arrhythmia, and whereas the immediate consequences of paroxysmal ventricular tachycardia are no different from those in the other arrhythmias under identical conditions, the mortality is highest in this group, probably on account of the seriousness of the underlying heart condition, or the conversion of the paroxysmal ventricular tachycardia into ventricular fibrillation.

The influence of the heart lesion and of the functional status of the circulation on the type of clinical response to paroxysmal rapid heart action is decisive, and may be best observed in cases of mitral stenosis, angina pectoris of effort and con-

gestive heart failure. The characteristic response in cases of compensated mitral stenosis consists of dyspnea, orthopnea, asthma, pulmonary edema and hemoptysis. These manifestations usually occur when the ventricular rate is 150 per minute or more; pulmonary congestion is not induced when the ventricular rate is well under this level, but is rarely absent when it is exceeded. These clinical phenomena, in some cases, may be less pronounced when, in addition to mitral stenosis, there is aortic valvular disease, congestive failure or vascular collapse. The clinical and x-ray manifestations of the pulmonary congestion disappear with remarkable rapidity when normal rhythm is resumed. A spontaneous diuresis may then be observed, even though there is a complete absence of manifest edema or other fluid accumulations (except in the lungs). The extent of the response, or the lack of it, depends not only on the ventricular rate but also on the degree of mitral stenosis.

In compensated valvular heart disease other than mitral stenosis, regardless of the ventricular rate, pulmonary congestion is not induced.

In cases of congestive failure and angina pectoris, as well as in cases of mitral stenosis, dyspnea may be one of the consequences of paroxysmal rapid heart action. When it occurs in angina pectoris, it accompanies anginal pain, which is the



leading symptom induced by the tachycardia, and is no different from the dyspnea experienced in attacks of angina that occur spontaneously or are provoked by effort. Similarly, in congestive failure, dyspnea, like the other manifestations of myocardial insufficiency, — congested liver, edema and so forth, — is increased in severity but is evident before the onset of the tachycardia.

Paroxysmal rapid heart action increases the severity of pre-existing congestive failure and may precipitate gross congestive failure in cases with limited cardiac reserve if the paroxysm is unduly prolonged or the ventricular rate is extremely rapid. When the paroxysms are transitory or the ventricular rates are considerably below 150 per minute, no effect on congestive failure is observed. The essential factor in this group of cases is not the type of heart lesion, but the functional status of the cardiovascular system. Embolism does not occur so preponderantly in cases of paroxysmal auricular fibrillation and of mitral stenosis when congestive failure is present as when it is absent. When symptoms are stated in publications concerning paroxysmal tachycardia, dyspnea or other manifestations of congestive failure are usually given a prominent place. Perusal of individual case reports often reveals the existence of mitral stenosis, congestive failure and angina pectoris. This coincides with my own findings, and these cases will not be reviewed here. There are, however, many case reports in which these conditions are not reported to be present, even though the clinical data are fully recorded, but in which dyspnea or other manifestations of congestive failure first appear after the onset of paroxysmal rapid heart action.<sup>2, 4, 7-9, 12, 14, 16, 18, 19, 21, 24-26</sup>

The cases referred to are selected as examples of dyspnea or congestive failure brought on by paroxysmal rapid heart action in patients who, prior to the onset of tachycardia, presumably had normal hearts; these furnish a striking contrast to the cases reported in this paper and indicate the need for careful observation of additional clinical material before the relation of dyspnea and failure to various factors can be fully expressed. From the recorded case histories, however, certain conclusions appear to be justified. There is a preponderance, in this group, of infants and young children. In most cases, the ventricular rates were extremely rapid, attaining or approaching the highest rates known to occur; in many, the paroxysms were unusually long. Infection preceding the onset of tachycardia was commonly observed, and was followed by clinical evidence of acute myocardial disease in some and by post-mortem demonstration of diffuse myocarditis in others. In some of the recorded cases, conditions besides car-

diac disease have been responsible for the occurrence of dyspnea. Finally, in most patients with extremely rapid heart rates, auricular flutter is responsible for the tachycardia; the extreme rate is due to a paroxysm of 1:1 ventricular response in the course of an established flutter.<sup>22</sup>

Patients who experience angina pectoris on effort invariably suffer similar attacks during paroxysms of rapid heart action, provided that the ventricular rate is 150 or more per minute; pain is never provoked if the rate is well under 150, unless digitalis has been taken. It is noteworthy that in cases of extensive coronary disease without angina pectoris, paroxysmal tachycardia, even with extremely rapid rates, does not induce anginal pain. Only occasionally does paroxysmal rapid heart action induce anginal pain in those who have never experienced angina on effort. This is true in elderly crippled patients whose activity is seriously hampered and, rarely, in those with aortic insufficiency; it may constitute a premonitory warning that acute cardiac infarction is soon to occur or is already in progress. Under the latter two conditions, the possibility that the paroxysm of rapid heart action has precipitated acute coronary thrombosis or cardiac infarction must be considered. Paroxysmal rapid heart action complicating acute cardiac infarction does not materially influence the pain, which may cease even though the tachycardia continues unabated.

When one appraises an attack of paroxysmal rapid heart action accompanied by angina pectoris (or status anginosus), two possibilities must be considered: the attack may represent the induction of angina by paroxysmal rapid heart action or acute coronary thrombosis or cardiac infarction may have taken place. If the history reveals the past occurrence of angina on effort, it is probable that the former situation prevails, notwithstanding the presence of fever, leukocytosis and even embolism; the pain, fever and leukocytosis (if there is no embolism) promptly disappear on cessation of the tachycardia. On the other hand, if angina on effort has never occurred, serious consideration must be given to the diagnosis of acute cardiac infarction. If the pain continues after normal rhythm has been resumed, if the pain disappears while the tachycardia remains in progress without a significant lowering of the ventricular rate, if there is vascular collapse despite a moderate ventricular rate, and if the temperature and white cell count do not rapidly revert to normal level on cessation of the tachycardia, it is highly probable that acute cardiac infarction has occurred. Rarely, paroxysmal rapid heart action may begin after the onset of angina pectoris, of which it is then a complication.<sup>27</sup>

The significance of the cardiac lesion is illustrated in those patients who have had paroxysmal tachycardia for a long time—in some cases twenty-five to fifty years. Repeated attacks may fail to induce symptoms until, years after the onset of paroxysmal rapid heart action, significant coronary-artery disease and angina of effort develop, with consequent induction of angina during paroxysms of tachycardia.

Three factors appear to be significant in the genesis of vascular collapse: extremely rapid ventricular rates, embolism and aortic valvular disease. Extremely rapid ventricular rates and embolism occur in half and one third of the cases, respectively. When extremely rapid ventricular rates are attained, all other factors may be absent, and the heart may be normal. If embolism complicates the tachycardia, the ventricular rate and the type of cardiac lesion are not significant. In the presence of aortic valvular disease, vascular collapse may occur, even though the ventricular rate is significantly under 150 per minute and embolism is absent. Although the 2 patients with slow ventricular rates were in congestive failure, it is unlikely that the latter is essential in the production of vascular collapse when the ventricular rate is slow; one patient had aortic valvular disease, and the other case was complicated by embolism. The age factor appears to be largely unimportant. Occasionally, in elderly patients, vascular collapse may occur with only moderately rapid ventricular rates, even though other contributing factors are not evident.

Cerebral manifestations are not uncommon. The age range in this group is higher than in the other groups, and the incidence of hypertension, congestive failure, embolism (or arterial thrombosis) and functional or organic cerebral disease is high. The events witnessed in this group are associated with various circumstances, which may be summarized as follows: Unconsciousness, with or without convulsions, may be provoked by a single factor,—extremely rapid ventricular rates or transitory cardiac standstill,—and may be seen in healthy young adults with normal hearts. When cerebral embolism complicates paroxysmal rapid heart action, loss of consciousness and convulsions or other cerebral manifestations may occur, regardless of the ventricular rate. In patients with functional nervous disorders or organic cerebral disease, paroxysmal arrhythmias with ventricular rates usually greater than 150 per minute may provoke confusion, irrationality or acute psychosis. It may therefore be stated that the induction of central nervous system manifestations depends on three factors: the ventricular rate, the "type" of patient and the organic cerebral disease. The type of heart lesion is not important, since patients

with normal hearts, as well as those with various types of heart disease, are seen in this group; the high incidence of hypertension and coronary-artery disease is probably explained by the frequency with which functional and organic cerebral disorders accompany these conditions. The best examples of cerebral manifestations are probably seen in cases with unusually rapid ventricular rates, as in auricular flutter with 1:1 ventricular response, when the rates approach  $300^{4, 6, 10, 11, 17, 22, 26-32}$ . On the other hand, even with extremely rapid ventricular rates, cerebral or other manifestations may be singularly absent.<sup>2, 6, 13</sup> Under cerebral manifestations, Barnes<sup>30</sup> includes vertigo, hemianopsia, temporary blindness, fainting, falling, with or without loss of consciousness, and epileptiform seizures.

Embolism may complicate any type of paroxysmal rapid heart action, occurring in patients of any age and with any type of heart disease. It is commonest in the presence of mitral stenosis and with auricular fibrillation. The most frequent consequences are circulatory collapse and dyspnea, the latter, in this series, occurring only in cases of mitral stenosis. The most frequent site of embolism is the lungs. Although embolism complicates the arrhythmia in most cases, the former may precede and provoke the latter, this sequence occurred in 1 case of auricular fibrillation and in 2 of auricular flutter.

Paroxysmal rapid heart action may cause death as the result of heart failure, vascular collapse, embolism, renal failure, the conversion of the paroxysmal arrhythmia into ventricular fibrillation, or cardiac standstill.

Paroxysmal auricular tachycardia may occur in patients who at other times exhibit carotid sinus sensitivity. Nevertheless, pressure exerted over the carotid sinus may not influence the paroxysm. In some cases, this failure of response may be associated with a marked fall in blood pressure, which accompanies the tachycardia, whereas in others the same phenomenon is observed even though a drop in blood pressure has not occurred.

The four types of paroxysmal rapid heart action with which this report is concerned were associated with many different extracardiac conditions, especially in the patients with normal hearts: gastrointestinal disturbances (including peptic ulcer, gall bladder disease, carcinoma, acute gangrenous appendicitis and incarcerated hernia), anesthesia, surgery, infections (pneumonia, peritonitis, pericarditis, acute mediastinitis, pulmonary tuberculosis, chronic pulmonary infections, pleuritis, wound sepsis, furunculosis and acute tonsillitis), lung tumor, embolism, trauma, carbon monoxide poisoning, exertion (including such activities as turning or twisting of the body, laughing and sneezing), emotional

upsets, hyperthyroidism, menopausal disturbances, acute yellow atrophy of the liver and the use of digitalis. The relation of many of these conditions to the inception of auricular fibrillation is discussed, and the literature reviewed, by Parkinson and Campbell.<sup>27</sup>

There is considerable experimental and clinical evidence that digitalis may provoke or prolong paroxysms of auricular fibrillation.<sup>17, 27, 33-39</sup> For this reason alone, one may doubt the advisability of routine digitalis therapy in such cases. Furthermore, the ventricular rate is not always rapidly controlled, and it is of greater fundamental value to abolish the abnormal rhythm. Digitalis is not indicated in paroxysms of auricular fibrillation when the ventricular rate is less than 150 per minute, and in any event, regardless of the rate, if symptoms are not provoked by the paroxysm. The wisdom of continually using digitalis for the avowed purpose of assuring a slow ventricular rate whenever a paroxysm of auricular fibrillation occurs may be seriously questioned on the basis of the evidence. In a considerable number of cases, under these circumstances, a ventricular rate sufficiently slow to prevent the development of symptoms is not achieved.

#### SUMMARY

The clinical data of 125 cases of paroxysmal rapid heart action are analyzed.

The cardinal symptoms and signs are correlated with certain significant variables in the individual patient. It has been shown that the various phenomena occurring in paroxysmal rapid heart action arise under definite conditions and relations and thus create, within broad limits, a uniform clinical pattern.

The cardinal manifestations of paroxysmal rapid heart action are palpitation, pulmonary congestion (dyspnea, wheezing, pulmonary edema and hemoptysis), angina pectoris or status anginosus, congestive failure, vascular collapse, cerebral manifestations and embolism. In many cases, no symptoms are provoked.

The significant variables are the type of patient, the heart lesion, the functional status of the circulation, the ventricular rate (and in a lesser degree the type of rhythm) and the presence or absence of embolism.

The most characteristic responses occur in cases of mitral stenosis, angina pectoris and congestive failure.

The critical level of the ventricular rate is approximately 150 per minute. As a rule, manifestations are not provoked below this level. The characteristic consequences of extreme rates are discussed.

The effect of digitalis on the ventricular rate in cases of paroxysmal auricular fibrillation is discussed.

270 Commonwealth Avenue

#### REFERENCES

1. Wolff, L. Angina pectoris (or status anginosus) and cardiac asthma induced by paroxysmal auricular fibrillation and paroxysmal tachycardia: the value of quinidine sulphate in the treatment of the conditions. *New Eng. J. Med.* 208:1194-1197, 1933.
2. Koplik, H. Paroxysmal tachycardia in children. *Am. J. M. Sc.* 154:851, 1917.
3. McMillan, T. M., and Sweeney, J. A. Auricular flutter, with period of 1:1 ventricular response. *Am. J. M. Sc.* 163:893-901, 1924.
4. O'Flynn, J. L. Paroxysmal tachycardia in an infant. *Brit. M. J.* 1:151, 1925.
5. Werley, G. Paroxysmal tachycardia, with ventricular rate of 307, in child four days old. *Arch. Pediat.* 42:825, 1925.
6. Lewis, T. *The Mechanism and Graphic Registration of the Heart*. 529 pp. London: Shaw and Sons, Ltd., 1925.
7. Farr, L. E., and Wegman, M. E. Extreme tachycardia in the newborn with report of a case. *Am. J. M. Sc.* 190:22-28, 1935.
8. Düken, J. Über eine typische Form der paroxysmalen Tachycardia im Säuglingsalter. *Arch. f. Kinderh.* 99:65-72, 1933.
9. de Bruin, M. Paroxysmale Tachycardia bei einem Säugling. *Nederl. tijdschr. v. geneesk.* 74:3415-3418, 1930.
10. Russell, H. B., and Ellison, J. B. A case of prolonged tachycardia associated with congenital heart disease, in a child fifteen months old. *Lancet* 2:546, 1927.
11. Scott, R. W. A case of auricular flutter with paroxysmal attacks of conduction. *J. A. M. A.* 79:1984-1987, 1922.
12. Lyon, J. A. Excessively rapid heart rates: report of a case with autep. *J. A. M. A.* 108:1393-1398, 1937.
13. Langley, R. W. Paroxysmal tachycardia with an unusually rapid heart rate in a boy of fourteen years. *Am. Heart J.* 3:368-371, 1928.
14. Bunn, W. H. Ventricular tachycardia, rate of 300, following thyroidectomy. *Am. Heart J.* 8:714-718, 1933.
15. White, P. D., and Stevens, H. W. Ventricular response to auricular premature beats and to auricular flutter. *Arch. Int. Med.* 13:712-716, 1916.
16. Blackford, J. M., and Williams, F. A. Auricular flutter. *Arch. Int. Med.* 21:147-165, 1918.
17. MacKenzie, J. *Diseases of the Heart*. Third edition. 502 pp. London: Oxford University Press, 1918.
18. Sachs, H. Zur paroxysmalen Tachycardia. *Zentralbl. f. Herz- und Kreislaufheilk.* 18:65-74, 1926.
19. Herapath, C. E. K. Auricular flutter. *Brit. M. J.* 1:213, 1928.
20. Colgate, C. F., and McCulloch, H. Paroxysmal tachycardia in infancy: report of two cases with comments on differential diagnosis. *Am. Heart J.* 2:160-165, 1926.
21. Clarke, T. W. Paroxysmal tachycardia in infancy. *Arch. Pediat.* 52:666-675, 1935.
22. Bedell, C. C. Auricular flutter with 1:1 response. *Bull. Johns Hopkins Hosp.* 52:225-254, 1933.
23. Arenberg, H. Paroxysmal auricular flutter with 1:1 auriculoventricular ratio. *Ann. Int. Med.* 8:951-958, 1935.
24. Hubbard, J. P. Paroxysmal tachycardia and its treatment in young infants. *Am. J. Dis. Child.* 61:687-709, 1941.
25. Shookhoff, C., Litvak, A. M., and Matusoff, I. Paroxysmal tachycardia in children: report of four cases and one postmortem examination. *Am. J. Dis. Child.* 43:93-122, 1932.
26. Wright, F. H. Paroxysmal nodal tachycardia treated with meclo. *Am. J. Dis. Child.* 56:1334-1341, 1938.
27. Parkinson, J., and Campbell, M. Paroxysmal auricular fibrillation: a record of two hundred patients. *Quart. J. Med.* 23:67-100, 1930.
28. Van Cleave, M. Paroxysmal tachycardia in an infant. *J. A. M. A.* 94:1758, 1930.
29. Sprague, H. B., and White, P. D. Auricular flutter: report of a case of five years' duration with spontaneous restoration of normal rhythm. *J. A. M. A.* 90:1772, 1928.
30. Barnes, A. R. Cerebral manifestations of paroxysmal tachycardia. *Am. J. M. Sc.* 171:489-495, 1926.
31. Parkinson, J., and Bedford, D. E. The course and treatment of auricular flutter. *Quart. J. Med.* 21:21-50, 1927.
32. Parkinson, J., and Mathias, H. Tachycardia of auricular origin: flutter with phasic variation in auricular rate and in conduction. *Heart* 6:27-36, 1915.
33. MacKenzie, J. Digitalis. *Heart* 2:273-369, 1911.
34. Cushman, A. R. Irregularity of the heart and auricular fibrillation. *Am. J. M. Sc.* 141:826-837, 1911.
35. Robinson, G. C. The influence of the vagus nerves on the faradic auricles in the dog's heart. *J. Exper. Med.* 17:429-443, 1913.
36. Andrus, E. C., Carter, E. P., and Wheeler, H. A. The refractory period of the normally-beating dog's auricle, with a note on the occurrence of auricular fibrillation following a single stimulus. *J. Exper. Med.* 51:357-367, 1930.
37. Nahum, L. H., and Hoff, H. E. Auricular fibrillation in hyperthyroid patients: produced by acetyl-B-methylcholine chloride, with observations on the rôle of the vagus and some exciting agents in the generation of auricular fibrillation. *J. A. M. A.* 105:254-257, 1935.
38. Gold, H., Kwit, N. T., Otto, H., and Fox, T. T. Physiological adaptations in cardiac slowing by digitalis and their bearing on problems of digitalization in patients with auricular fibrillation. *J. Pharmacol. & Exper. Therap.* 67:224-238, 1939.
39. Altschule, M. D. The relation between prolonged P-R interval and auricular fibrillation in patients with rheumatic heart disease. *Heart J.* 18:1-7, 1939.

## MEDICAL PROGRESS

### THE CHEMICAL MEASUREMENT AND CONTROL OF CLINICAL VITAMIN DEFICIENCY\*

WILLIAM T. SALTER, M.D.†

NEW HAVEN, CONNECTICUT

THE past decade has contributed not only a more detailed description of clinical deficiency disease, including several syndromes and symptoms hitherto unrecognized in man,<sup>1</sup> but also significant advances in the knowledge of the chemical nature of these interesting accessory food substances. In general, gross vitamin deficiencies continue to be diagnosed through the aid of the five senses, in addition to common sense. Nevertheless, the use of objective tests is desirable for three purposes: to confirm clinical diagnosis and so maintain a high standard of accuracy therein; to serve as a court of appeal in doubtful cases, particularly in the region of partial vitamin collapse that Minot<sup>2</sup> has termed the "twilight zone of vitamin deficiency"; and to check the effectiveness of therapy. The need for the first of these objectives is obvious. The need for the last two is becoming clearer as physiologic studies are demonstrating that vague apathies and lack of efficiency are produced by incipient vitamin lack, which causes symptoms commonly known as "subclinical." For example, for many years it has been known that a patient with pellagra may show no *pelle agra* until exposure to actinic rays is used to bring out the peculiarity of the condition.

In the field of neuropsychiatry, in particular, the lack of vitamin B complex is becoming more and more important. Thus, Jolliffe and his associates<sup>3</sup> have demonstrated that on a thiamin-deficient diet healthy interns in a hospital underwent a considerable loss of "energy" and even showed changes in personality within a relatively few days. Indeed, many patients in severe illness are subject to a lack of vitamin intake not unlike that which these experimental observations produced, and it remains to be seen to what extent severe or debilitating disease produces a similar change in personality through lack of these essential substances. In the intricate fields of neurasthenia and psychoneurosis, this problem may also complicate the picture. For this reason, there is a wide opportunity for the use of chemical methods

in the investigation of routine patients, even those whose symptomatology is not very dramatic. Such determinations, of course, should not replace careful dietary histories or painstaking physical diagnosis. They should be used in a confirmatory sense.

With the development of knowledge concerning the nature of the vitamins have come appropriate chemical methods for their determination. These chemical procedures are far more practical and convenient than the older mammalian assays, which are so costly and time-consuming that for clinical purposes they are not practical. To be sure, they may still be used occasionally to check the chemical methods employed for clinical purposes. Likewise, in recent years, the use of micro-organisms for biologic assay has extended the practicability of the biologic method for testing vitamin concentration. For example, in the assay of biotin, the vitamin universally needed for growth, it is possible to measure extraordinarily small amounts of material. One makes the measurement by studying the effects on the growth of micro-organisms of amounts of this substance that are of the order of a small fraction of a millionth of a gram. If, however, practical application in clinical cases is to be hoped for, it will probably come chiefly through the use of chemical tests.

Two main difficulties have stood in the way of the development of such reactions. The first is that such extraordinarily minute amounts of the material are needed in nature; this follows from the fact that the vitamins in general are to be thought of as natural catalysts. Indeed, some of them are known to contribute the precise prosthetic groups that determine the specificity of enzymes. In this respect, they are analogous to the haptophore groups that Ehrlich postulated for antibodies. The second difficulty is that, obviously, to detect such small amounts of material by a practical chemical procedure, one often has to sacrifice a certain degree of specificity. Therefore, so far as chemical specificity has been sacrificed, the method is subject to error. In spite of these difficulties, tests are already available that can be used in clinical cases; they are simple enough to be performed in any large clinic that has in operation research laboratories for routine clinical studies.

Reprints of articles in this series are not available for distribution but the articles will be published in book form. The current volume is *Medical Progress: Annual, 1940* (Springfield, Illinois: Charles C. Thomas Company, 1941, \$4.00).

\*This Yale University School of Medicine Professor

†Professor of pharmacology, Yale University School of Medicine.

Several of the vitamins have been discovered so recently that as yet their detection is largely a biologic affair. Accordingly, it is not practical to expect their analysis in clinical cases for some time. Of the better known vitamins, however, simple chemical methods have now been developed for carotene and vitamin A, for thiamin, for riboflavin, for ascorbic acid and for nicotinic acid. Fortunately, it is becoming progressively clearer that vitamin deficiency, as it is encountered clinically, is usually multiple. Accordingly, in many cases, if one detects the lack of one of these well-known vitamins and thus confirms the noncommittal diagnosis of "vitamin deficiency," there are likely to be deficiencies of other vitamins not specifically tested. For this reason, the administration of the one pure vitamin recognized as lacking in a given case may remedy only part of the patient's difficulty. If, however, a well-balanced diet is included in the therapeutic regimen, natural food-stuffs will probably correct any serious deficiency of some of the less well-known vitamins. More experience is needed in this field, but it is already clear, for example, that in clinical pellagra there is a deficiency, usually of nicotinic acid, but frequently also of thiamin or riboflavin. Indeed, these secondary deficiencies account for the wide differences in symptomatology and in response to therapy of individual cases.

#### TECHNICAL POSSIBILITIES

In general, two main procedures are available for detecting vitamin deficiency chemically—the first, through the determination of the concentration of vitamin in the blood, and the second, through the study of urinary excretion. At one time, it was thought that a low vitamin concentration in the blood strongly indicated a vitamin deficiency. This is now known not necessarily to be so. For example, the investigations of Mindlin and Butler<sup>4</sup> have shown that the vitamin C content of the plasma may undergo considerable fluctuations for a short time in fairly normal subjects, and that the plasma level may drop to very low concentrations while the tissue reservoirs of vitamin are still entirely adequate. It may be said, therefore, that whereas a high vitamin level in the blood ordinarily rules out deficiency of the antiscorbutic vitamin, a low level does not necessarily mean that the patient's tissues are really suffering from its lack. Furthermore, with the other vitamins, a normal blood concentration may exist in the presence of undoubted deficiency, as will be explained presently.

In such cases, the study of urinary secretion is of more value. To be sure, collection of urine involves extra work, and is subject to the errors of decomposition and loss. Nevertheless, if one finds

that a patient is still excreting considerable amounts of vitamin in the urine, one is assured that there is an excess of that vitamin in the organism. On the contrary, if the vitamin excretion is low, one may assume that no such excess of the essential factor exists. Furthermore, urinary studies may be extended by the use of the so-called "vitamin-tolerance test." In this technic, a known amount of vitamin is administered, and its fate by urinary excretion is subsequently determined. If the tissues have been hungry for vitamins, they will retain a large portion of the vitamin administered. If, on the other hand, the tissues have already been replete with vitamin stores, they will fail to retain so considerable a portion of the vitamin administered.

In such a test, if the vitamin is administered orally, one must take special precautions to exclude conditions that would interfere with the absorption of the vitamin by the alimentary tract. The same precautions hold for subcutaneous administration in edematous patients. On the other hand, it is not always desirable to administer vitamins by vein. For example, even in vitamin-deficient persons, if thiamin is administered intravenously, a large amount may run out through the kidneys before the tissues have a sufficient opportunity to affix the thiamin. It will be apparent that it is easier technically to rule out vitamin deficiency than to verify it, and that whenever such a test reveals vitamin deficiency, the technic must be scrutinized carefully and the test repeated, to exclude, so far as possible, technical errors such as those discussed.

#### ANALYTICAL METHODS

So far as the chemical procedures now available are concerned, it must be remarked at the outset that there are frequently two or more competing methods for the determination of a given vitamin. In certain cases, one must weigh the expense of a complicated apparatus like a spectrophotometer against excessive labor costs or fatigue when a more tedious procedure is used. In other cases, a test requiring a considerable degree of skillful technical manipulation may have to be abandoned in favor of a simpler but more costly one. For this reason, the choice of the methods mentioned below is at best arbitrary, but in my opinion and that of my associates, they offer the best compromise between the various factors described.

Whatever method is chosen, it is always well to repeat the determination in cases suggesting vitamin deficiency before administering therapy, and to repeat the test at various intervals after the therapy is begun. This is especially desirable in cases in which the so-called "conditioned vitamin deficiency" is suspected. This sort of de-

ciency, which occurs when the dietary history is apparently adequate, has been described by Strauss,<sup>5</sup> Richardson<sup>6</sup> and Salter.<sup>7</sup> It is particularly common, as Castle et al.<sup>8</sup> have pointed out, in conditions involving the gastrointestinal tract. In these cases, owing to failure of absorption, the tissues suffer from vitamin lack although the diet contains an adequate amount of vitamin. If, in such circumstances, chemical responses in blood or urine can be recognized when the vitamin is administered, and especially if clinical improvement occurs simultaneously, the chance of error can be greatly reduced.

One further complication that may be encountered is the problem of the provitamin, of which carotene is a classical example with reference to vitamin A. Moore<sup>9</sup> and others have shown that crystalline carotene, although not in itself a vitamin, relieves vitamin A deficiencies and causes vitamin A to increase in concentration in the body fluids and in tissues like the liver. In the analysis of foodstuffs, therefore, the content of provitamin may be more significant than that of the vitamin itself. Nevertheless, in the body fluids or tissues, the vitamin is ordinarily the important form in relation to deficiency disease.

#### VITAMIN A

Although the existence of vitamin A has been known for many years and its relation to carotene studied carefully, practical methods for the quantitative determination of this vitamin in human blood are only in a preliminary stage. The detection of vitamin A deficiency by the use of biophotometers for night blindness, or hemeralopia, has had a vogue in recent years, but it has become apparent that this method is fraught with many complications. Accordingly, investigators are turning back to the direct measurement of vitamin A in serum or plasma to determine a deficiency of this vitamin. In general, the tests are based on two optical procedures: the colorimetric and the spectrometric.

The first of these utilizes the classic Price-Carr blue reaction, which the vitamin gives with antimony trichloride under certain conditions. The difficulty is that this color is evanescent and is not altogether specific for vitamin A. Some of the difficulties involved have been summarized by Lindqvist.<sup>10</sup> Because of these obstacles, Munsell<sup>11</sup> thinks that the spectrometric method of analysis holds more promise. Nevertheless, by the use of the photoelectric colorimeter or a step-photometer, it has been possible already to analyze the plasma or serum of the blood under different conditions. The results are apparently consistent within themselves, although there is a considerable difficulty in any investigation in converting the values given back into absolute terms.

Accordingly, at present, many clinical values are merely stated in "blue units" to indicate that the conversion factor of these units in actual concentrations is a matter of conjecture. Nevertheless, as reported by Pett and LePage,<sup>12</sup> within four hours after the ingestion of 20,000 international units of vitamin A, the plasma "blue unit" value rose from 76 to 133 international units. The rise indicated that about 10 per cent of the vitamin administered was in the circulation. The authors found that 88.0 microgm. of beta-carotene gave the same blue color as 84.1 international units of vitamin A. Accordingly, some method of correction must be made for the carotene test. The carotene, however, can be determined by other methods, the simplest of which makes use of the characteristic yellow color of this substance.

In his comprehensive monograph on the absorption, metabolism and storage of vitamin A and carotene, With<sup>13</sup> has discussed the behavior of these absorptive bands toward ultraviolet light from the standpoint of routine analytical procedures. He emphasizes the great variation in the conversion factors found by independent investigators. The same author has also collected many valuable data on the metabolism of these two related substances. He points out that normal subjects most frequently show a serum carotenoid concentration of between 20 and 50 microgm. per 100 cc. Values over 100 microgm. are rare. In the blood from the umbilical cord, however, values of about 10 microgm. are ordinarily found. The carotene content of serum, expressed as percentage of the total carotenoid, is highly variable. It ranges from one tenth to one half of the total.

Only rarely does vitamin A pass through the kidney into the urine. Pregnancy may be an exception; likewise, the urine may contain vitamin A in cases of infectious disease, liver lesions, malignant tumors and diabetic acidosis. In such cases, perhaps, it is combined with abnormal excretory substances.

Tolerance tests give, as they are applied at present, no information about the carotenoid or vitamin content of the organism.

The photometric technic has been applied in a number of interesting clinical conditions. For example, May and McCreary<sup>14</sup> have used a photometric method reported by Dann and Evelyn<sup>15</sup> to determine the vitamin A content of serum in celiac disease. Clausen and McCoord,<sup>16</sup> using a similar method, found that the mean vitamin A was 20.2 U.S.P. units per 100 cc. of plasma; the standard deviation was 10 units. Pett and LePage<sup>12</sup> obtained values in relatively normal subjects ranging from 50 to 90 international units per 100 cc. of plasma. These data showed a good correlation with visual tests. In natives of Batavia suffering

from xerophthalmia, deHaas and Meulemans<sup>17</sup> observed no more than a trace of vitamin A in the serum. Similarly, Clausen and McCoord<sup>16</sup> found that infection caused a prompt fall in the concentration of carotene and vitamin A in the plasma. Similar studies have been made by Wilbur<sup>18</sup> in adults and by May, Blackfan, McCreary and Allen<sup>19</sup> in children.

Somewhat paradoxical results have been found in diseases that involve disturbances of lipid metabolism. For example, in hypothyroidism, the content of the plasma may be low in vitamin A, returning to normal after thyroid therapy. In Bright's disease, however, the level may be greatly elevated. This observation is consistent with the effects noted by Josephs,<sup>20</sup> who made correlative studies of the blood levels of vitamin A, carotene, cholesterol and blood fat. He concluded that there is a direct relation between vitamin A, carotene and the total lipids of the blood. Indeed, the highest carotene and vitamin A values in his series were found in conditions associated with lipemia, that is, hypothyroidism, nephrosis and xanthomatosis. His lowest values were obtained in infants with pneumonia, and in patients with cardiac decompensation or with evidence of other deficiencies. In cases of pneumonia with low values for vitamin A, low values for total lipids were also found. This was true also of the cardiac cases, but not in cases of dietary deficiencies.

Of special interest is the finding by Abels, Gorham, Pack and Rhoads<sup>21</sup> of low levels of plasma vitamin A in patients with cancer of the gastrointestinal tract. Their results may be related to studies of cirrhosis of the liver by Ralli, Bauman and Roberts.<sup>22</sup>

In summary, it may be said that with the introduction of more precise optical apparatus, such as the spectrophotometer, there is a high likelihood that relative values for vitamin A and for carotene will be available and that such values will have a very important pathognomonic significance. It will be difficult to have absolute accuracy, but this goal is not beyond expectation in the near future. Such methods bid fair to supersede the visual tests as measures of vitamin A deficiency. At the present time, however, it must be admitted that this field is just being developed by clinical investigators.

#### THIAMIN (VITAMIN B<sub>1</sub>)

Several methods applicable on a clinical scale have been proposed for the estimation of thiamin. Notable among these are two that involve the use of micro-organisms. For example, Light, Schultz, Atkin and Cracas<sup>23</sup> used a fermentation test for vitamin B<sub>1</sub> that is applicable to many prob-

lems.<sup>24, 25</sup> Likewise, the growth of phycomyces has been applied by Schopfer<sup>26</sup> and Meiklejohn.<sup>27</sup> More convenient, however, are chemical procedures, notably the thiochrome assay of Jansen<sup>28</sup> and the test of Prebluda and McCollum.<sup>29</sup>

In the latter method, which has been applied extensively by Melnick and Field,<sup>30</sup> the urine or other material to be analyzed is first extracted with benzyl alcohol. The reaction between the vitamin and diazotized para-aminoacetophenone, described by Melnick and Field,<sup>31</sup> is the basis for the determination. This method is highly accurate and specific, but the technic is rather complex for ordinary clinical purposes. In general, I prefer tests based on the thiochrome conversion of Jansen, the principle of which is the oxidation of thiamin to thiochrome by an appropriate amount of ferricyanide in strongly alkaline solution. Jansen has shown that a quantitative, although not complete, conversion into thiochrome occurs under appropriate conditions. Thiochrome has the property of fluorescing as an intense blue color in ultraviolet light. The intensity of the fluorescence depends on the amount of thiochrome present. This may be measured either with a photoelectric cell or by direct visual comparison with a series of standard tubes.

The technic of this reaction has recently been surveyed by Egaña and Meiklejohn,<sup>32</sup> who point out that a preliminary extraction with isobutyl alcohol removes many interfering substances. The technic is complicated somewhat by the fact that certain interfering substances in pathologic urine hinder the recovery of the thiamin as thiochrome and so tend to exaggerate a paucity of the vitamin in urine from patients exhibiting profound disturbance of metabolism. Nevertheless, this method is now properly adapted for clinical observation. For a normal subject placed on a low thiamin diet, Egaña and Meiklejohn have found that in the course of a fortnight the twenty-four-hour excretion of the vitamin decreases from over 100 microgm. daily to less than 10. At this point, the urine is obviously pathologic. It may contain albumin, casts or blood, and certain chemical substances probably related to porphyrins or to indoxyl.

In my laboratory a twenty-four-hour urinary excretion of less than 70 microgm. of thiamin, as determined by the thiochrome method,<sup>32</sup> is considered *prima-facie* evidence of undoubted deficiency. Possibly this arbitrary value should be higher for men.

It is impossible to discuss the physiology of thiamin metabolism in this article, but a few illustrative results may be cited to indicate how the method may be applied clinically. Westenbrink

and Goudsmit<sup>33</sup> found that the urinary excretion of the vitamin depended on the amount injected. On a deficient diet, the urinary excretion decreased to a low level within three days. Likewise, Jowett<sup>34</sup> studied fractional urinary excretion following the administration of a known amount of vitamin. In normal subjects, the excretion for twenty-four hours varied from 80 to 300 microgm., and the great majority of cases showed over 100 microgm. for twenty-four hours' urine. When 3 to 5 mg. of pure thiamin was administered by mouth, the urine increased in concentration within the first hour after the administration, reached a peak between the second and fourth hours, and approached the normal level in about five hours. When larger doses were given, the increased excretion might extend into the second day. Furthermore, the percentage excreted depended on the size of individual doses rather than on the total dose given a day. It is interesting that intramuscular injections gave a maximal excretion during the first hour, and thereafter an excretion corresponding to that following oral administration. Curiously enough, these parenteral test doses disclosed no difference between normal and thiamin-deficient subjects, and the parenteral method was therefore considered to be of little value in differentiating normal persons from those suffering from lack of the vitamin. Pregnancy decreased the excretion of the vitamin, even in the absence of demonstrable clinical vitamin deficiency.

Obviously, the activity of the gastrointestinal tract modifies these responses considerably. Thus, Ritsert<sup>35, 36</sup> found a high fecal excretion amounting to 100 to 400 microgm. of thiamin in twenty-four hours in normal men. Indeed, after a single 10-mg. dose of thiamin, only about 5 per cent was found in the urine, whereas over 20 per cent was found in the feces. Obviously, much thiamin was not absorbed. Other factors no doubt enter into the picture. For example, Melnick, Field and Robinson<sup>37</sup> have found that vitamin B<sub>1</sub> is unstable in alkali and that, at the alkalinity of the small intestine, thiamin is slowly destroyed. In patients with ulcerative colitis and diarrhea, absorption is also poor.

The oral thiamin-tolerance test has been made use of by several investigators. Among these, Borson,<sup>38</sup> Melnick, Field and Robinson,<sup>37</sup> Westenbrink and Goudsmit<sup>33</sup> and Jowett<sup>34</sup> have reported interesting results. If gastrointestinal disease can be excluded, it is assumed that the recovery in the urine represents a measure of the degree of unsaturation of the patient's tissues. Accordingly, the percentage excreted is inversely proportional to the size of the dose given by mouth. The extent of the deficiency may be estimated in two ways:

either by determination of the number of daily doses required for the excretion to rise to normal, or by observation of the amount failing to be excreted after a single large dose. In this way, Westenbrink and Goudsmit found that the urine normally contains over 100 microgm. a day. When 3 to 5 mg. of thiamin is given,—preferably with a morning meal,—urinary excretion is increased in one hour, reaches a peak at about three hours, and returns to normal at five hours. Occasionally, doses as large as 100 mg. are given to patients, but probably over 90 per cent of such a large dose fails to be absorbed or is destroyed in the intestine.

By these methods, definite deficiency may be detected in many chronic diseases, including thyrotoxicosis, multiple sclerosis, neuritides of various types, central-nervous-system syphilis and certain neurasthenias. Ulcerative colitis likewise tends to show a low excretion. In normal pregnancy, the urinary excretion tends to fall, even in the absence of disease or true deficiency. Furthermore, in this laboratory, Dr. R. C. Roskelley<sup>39</sup> has found that a considerable percentage of cancer patients show thiamin deficiency even though they may present a clinical appearance of fair nutrition.

An approximate conception of this difference between the composite thiamin-tolerance curves of 14 noncancerous and 10 cancerous patients may be formulated by plotting against the time in hours (abscissa) the rate of urinary thiamin excretion in micrograms per hour (ordinate). The following abscissas should be plotted for time (hours): 0, 2, 3, 4, 5, 6, 8 and 24. The corresponding ordinates for noncancerous persons are 4, 72, 226 (peak), 95, 88, 53, 16 and 10. The corresponding ordinates for cancerous patients are 7, 26, 46 (peak), 32, 27, 24, 14 and 9. When these two composite curves are plotted, the striking difference in their respective heights will be apparent at once. It should be noted that these curves were obtained by the feeding of 5 mg. of thiamin with a meal, usually breakfast.

Of course, many cancerous patients encountered in a general clinic suffer from thiamin deficiency per se, as evidenced by a preliminary thiamin excretion of less than 70 microgm. per twenty-four hours. Obviously, such patients show a low tolerance curve. The data summarized in the preceding paragraph, however, were derived from patients whose preliminary thiamin excretion was in all cases greater than 70 microgm. per twenty-four hours; therefore, the flat curve for cancerous persons is especially interesting and merits careful investigation of the mechanism involved.

Similarly, O'Shea-Elsom and Machella,<sup>40</sup> in a study of vitamin retention in patients with hepatic cirrhosis, found some diminution in the excretion



of extra thiamin. The cause of this, however, they attributed to faulty absorption.

### Blood Thiamin

It is interesting that under normal conditions very little pure thiamin is found in the blood, in either the cells or the plasma. Indeed, the plasma seems devoid, or nearly so, of any thiamin derivative. The red cells, however, contain definite amounts of the enzyme cocarboxylase, which was first identified chemically as thiamin-pyrophosphate by Lohmann and Schuster.<sup>41</sup> Even after the administration of thiamin chloride by vein, in the course of ten minutes to an hour, the material disappears from the plasma. This is true because much of the vitamin escapes into the urine, and also because it is converted in large measure into cocarboxylase. Simultaneously, there is a rise in the cocarboxylase content of the red cells. Methods are available for estimating this cocarboxylase concentration,<sup>42</sup> but as yet they have not been applied extensively to clinical patients.

In a procedure recently developed by Egaña,<sup>43</sup> the blood diphosphothiamin and the thiamin itself are determined after separate conversion into thiochrome. In normal persons, Egaña finds that the diphosphothiamin level in whole blood is 7.0 to 8.5 microgm. per 100 cc. He finds no coenzyme in the plasma. The free thiamin reaches a concentration of 3.5 to 4.2 microgm. per 100 cc. of whole blood, and is present in both cells and plasma.\*

### RIBOFLAVIN (VITAMIN B<sub>2</sub>)

Riboflavin possesses several characteristic properties that are useful in its estimation. For example, Kuhn, György and Wagner-Jauregg<sup>44</sup> demonstrated that pure riboflavin gives off a yellow-green fluorescence on activation by light of certain wave lengths. This property has been used extensively in the estimation of the vitamin. It is also possible, as shown by Koschara,<sup>45</sup> to measure the vitamin concentration by the direct measurement of its color or light absorption. This method, however, has found less favor than the fluorescent one, in which the final concentration of the vitamin is determined either by comparison with a direct series of standards under monochromatic ultraviolet light or, more effectively, by the use of a fluorophotometer. Because riboflavin is sensitive to light, it is essential that examination of the vitamin be carried out under controlled illumination. Various procedures have

been used in the preparation of the final filtrate for the determination. Indeed, the vitamin has been measured by its color, by the use of a spectrophotometer, by its fluorescence in aqueous solutions, by the color of its derivative, lumiflavin, dissolved in chloroform, and by the polarograph method. Most of these involve preliminary extraction of the vitamin. Najjar<sup>46</sup> has described one of the more useful of these procedures. He adds pyridine to the urine or other aqueous medium under investigation, and then separates the pyridine by salting out with anhydrous sodium sulfate. The separating pyridine contains practically all the riboflavin. Ultimately, the vitamin is extracted into butyl alcohol and measured in a fluorophotometer illuminated by a mercury-vapor bulb.

Likewise, Hodson and Norris<sup>47</sup> extracted the riboflavin in 0.25 normal sulfuric acid, and subsequently subjected the solution to treatment with sodium hyposulfite and stannous chloride at pH 7.

After a suitable extract is made, it is usually necessary to remove the vitamin selectively by adsorption. Accordingly, Ferrebee<sup>48</sup> introduced two preparations of fuller's earth, known as Floradine and Supersorb, respectively. Elution from these adsorbants was accomplished with a solution of 20 per cent pyridine in 2 per cent acetic acid. Even at this stage, however, the filtrate contains pigments that interfere with optical measurements. To remove such interfering substances, the eluate may be treated with an oxidizing agent, for example, potassium permanganate or hydrogen peroxide. A convenient modification of these methods that combines the determination of riboflavin and thiamin in food products has been described by Conner and Straub.<sup>49</sup> The riboflavin content of the solution is determined as follows:

After elution of the uroflavin and subsequent oxidation to decolorize the solution, the solution is made up to volume with water, and the fluorescence measured with an exciting mercury-line beam at 4358 angstroms. The fluorometric photoelectric cells should be protected by a filter, described by Conner and Straub.<sup>49</sup> Turbidity of the solution or a gaseous emulsion must not be present. Under these circumstances, the relation between the fluorescence and riboflavin concentration is a linear one when suitable corrections are made for optical densities.

The urines of normal subjects frequently contain more than half a microgram of flavin per cubic centimeter,<sup>50</sup> and under these circumstances the urine may be diluted to the point where salts and other materials present no longer affect the fluorescence, as shown by Kuhn and Moruzzi.<sup>51</sup> After interfering substances have been oxidized according to Koschara's<sup>45</sup> procedure, the fluorescence may be measured at once. When the urine is more dilute in vitamin, some preliminary con-

\*While this article was in press, there appeared two papers by Rhoads and his collaborators<sup>50, 51</sup> on the thiamin content of blood in leukemic patients. In this disturbance, the leukocytes and erythrocytes contain an abnormally high concentration of "combined thiamin." Consequently, the total thiamin content of the whole blood is approximately three times the normal. The ultimate significance of this important finding is not yet established. Certain cases of Hodgkin's disease and cancer of the gastrointestinal tract behave similarly.

centration of the uroflavin is necessary, such as that accomplished by the methods of Ferrebee<sup>48</sup> and of Conner and Straub,<sup>49</sup> already cited.

As a qualitative check for the presence of riboflavin, the uroflavin may be converted into lumiflavin by the action of light in cold, strongly alkaline solutions. Under these circumstances, a chloroform-soluble pigment that shows a faint green fluorescence is formed. This method is as yet in the early stages of development.

Henry, Houston and Kon<sup>52</sup> have compared the biologic method of assay of riboflavin with the fluorometric assay and have found good agreement in various milk products. So far as other methods of assay are concerned Arnold, Lipsius and Greene<sup>53</sup> have tested the microbiologic procedure of Snell and Strong,<sup>54</sup> which is based on the influence of this substance on the growth of *Lactobacillus casei*. This method is tolerably specific and much quicker than the rat-assay method, and can be carried out with very small amounts of material. The twenty-four-hour excretion of riboflavin in normal subjects varies from 700 to 1700 microgm. In general, as shown by Emmerie,<sup>55</sup> urinary excretion tends to follow the riboflavin content of the diet.

#### *Physiologic Role of Riboflavin*

It is known that riboflavin when phosphorylated, that is, when combined with phosphate, is utilized as the prosthetic group for several tissue-enzyme systems that are important in biologic oxidation. Some of these are described by Karrer et al.<sup>56</sup> Well-known metabolites, such as lactic acid, the  $\gamma$ -amino-acids and glucose, depend in part on this combined vitamin for their utilization in bodily economy. For these reasons, human illness can result from lack of the vitamin. As yet, however, no extensive study has been made of its clinical applications. Sebrell<sup>57</sup> calls attention to the prevalence of vitamin B<sub>2</sub> deficiency associated with other deficiencies, notably that of nicotinic acid. In these conditions, the relief of such lesions as the vascularization of the cornea and the healing of fissures of the mouth—the so-called “perleche”—often depend on the supply of vitamin B<sub>2</sub>. These lesions are not relieved by either thiamin or nicotinic acid. At the moment, however, no clear-cut clinical pathologic entity unaccompanied by manifestations of other vitamin deficiency is generally recognized as specifically requiring riboflavin for therapy without other vitamins. In the mixed vitamin deficiencies, fortunately, diets that contain thiamin or nicotinic acid usually supply adequate riboflavin.

Nevertheless, there are available certain interesting observations in man that will serve as a background for future clinical studies. For example, after the oral administration of some 200 mg. of riboflavin, Klein and Kohn<sup>58</sup> recovered about 25 per cent from the urine as riboflavin. At the same time, the dinucleotide concentration in the erythrocytes was approximately 30 microgm. per 100 cc. However, the actual concentration of the flavin-adenine dinucleotide in urine and saliva after such a large injection of riboflavin was less than 1 microgm. per 100 cc. Obviously, the dosage given in this case must be considered unusually high, because Cowgill<sup>59</sup> has estimated the daily requirement of riboflavin at from 1 to 2 mg. a day for an adult. Stiebling and Phipard<sup>60</sup> have confirmed this value.

#### *Blood versus Urinary Riboflavin*

Axelrod, Spies and Elvehjem<sup>61</sup> have found that in normal subjects blood riboflavin values range between 35 and 45 microgm. per 100 cc. Surprisingly enough, approximately the same blood values were found in a group of patients with riboflavin deficiency. Apparently, the determination of the riboflavin concentration in blood or muscle is of little significance in evaluating riboflavin deficiency in man. Accordingly, it is preferable to use urinary excretion. Thus, Strong, Feeney, Moore and Parsons<sup>62</sup> found that the daily urinary excretion of riboflavin by normal human adults was between 500 and 800 microgm. a day. When the dietary content of riboflavin was reduced to 1 or 2 mg. a day, the urinary value soon decreased to 50 to 150 microgm.

When 5 mg. daily was given supplementary to the diet, most of it was excreted promptly. However, in the presence of vitamin deficiency, no extra vitamin was excreted in response to the reinforcement of the diet, or else the response was small and delayed. Here again, one finds that the vitamin tolerance or vitamin retention, as with thiamin, is a better and more convenient index of vitamin lack than direct determinations in the blood.

Although much further clinical work needs to be done with this vitamin, it seems likely that tolerance tests for its lack are useful in obscure cases of ophthalmologic or dermatologic nature. It is also probable that such a test may be valuable in cases of vague neurologic or psychic disturbance. It remains to be seen what the status of this vitamin is in cancer. The work of Rhoads and his co-workers<sup>63, 64</sup> suggests that this vitamin may be implicated in cancer of the liver, if not in other malignant processes. To test this point, tolerance

tests involving riboflavin are being made in this laboratory by Dr. Roskelley. It is apparent that patients with cancer may suffer from such vitamin deficiency, but the implications of this fact are not yet clear.

(To be concluded)

## REFERENCES

1. Wilson's Symposium on Vitamins and Enzymes. Held under joint auspices of University of Wisconsin and University of Chicago, September, 1941. Madison: University of Wisconsin Press (in press).
2. Minot, G. R. Personal communication.
3. Jolliffe, N., Goodhart, R., Gennis, J., and Cline, J. K. The experimental production of vitamin B<sub>1</sub> deficiency in normal subjects. The dependence of the urinary excretion of thiamin on the dietary intake of vitamin B<sub>1</sub>. *Am. J. M. Sc.* 198:198-211, 1939.
4. Mindlin, R. L., and Butler, A. M. The determination of ascorbic acid in plasma: a macromethod and a micromethod. *J. Biol. Chem.* 122:673-686, 1938.
5. Strauss, M. B. The role of the gastro-intestinal tract in conditioning deficiency disease. *J. A. M. A.* 103:1-4, 1934.
6. Richardson, W. Pernicious anemia due to enterocystostomy: report of case cured by reoperation. *New Eng. J. Med.* 218:374-376, 1938.
7. Salter, W. T. Quantitative aspects of vitamin requirement. *J. Am. Dietet. A.* 10:296-308, 1934.
8. Castle, W. B., Heath, C. W., Strauss, M. B., and Townsend, W. C. The relationship of disorders of the digestive tract to anemia. *J. A. M. A.* 97:904-907, 1931.
9. Moore, T. Vitamin A and carotene. VI. The conversion of carotene to vitamin A *in vivo*. *Biochem. J.* 24:696-702, 1930.
10. Lindqvist, T. Studien über das Vitamin A beim Menschen. *Acta med. Scandinav. Suppl.* 97, 1938. 314 pp.
11. Munsell, H. E. Vitamin A: methods of assay and sources in food. *J. A. M. A.* 111:245-252, 1938.
12. Pett, L. B., and LePage, G. A. Vitamin A deficiency. III. Blood analysis correlated with a visual test. *J. Biol. Chem.* 132:585-593, 1940.
13. With, T. K. *Absorption, Metabolism and Storage of Vitamin A and Carotene, with Some Remarks on the Vitamin A Requirement.* Translated by Hans Andersen. 263 pp. London: Oxford University Press, 1940.
14. May, C. D., and McCreary, J. F. Absorption of vitamin A in celiac disease: interpretation of vitamin A absorption test. *J. Pediatr.* 18:200-209, 1941.
15. Dann, W. J., and Evelyn, K. A. The determination of vitamin A with the photoelectric colorimeter. *Biochem. J.* 32:1008-1017, 1938.
16. Clausen, S. W., and McCoord, A. B. The carotinoids and vitamin A of the blood. *J. Pediatr.* 13:635-650, 1938.
17. deHaas, J. H., and Meulemans, O. Vitamin A and carotinoids in blood: deficiencies in children suffering from xerophthalmia. *Lancet* 1:1110, 1938.
18. Wilbur, D. L. Diseases of metabolism and nutrition. II. Nutrition. *Arch. Int. Med.* 63:385-427, 1939.
19. May, C. D., Blackfan, K. D., McCreary, J. F., and Allen, F. H., Jr. Clinical studies of vitamin A in infants and in children. *Am. J. Dis. Child.* 59:1167-1184, 1940.
20. Josephs, H. W. Studies in vitamin A: relation of vitamin A and carotene to serum lipids. *Bull. Johns Hopkins Hosp.* 65:112-124, 1939.
21. Abels, J. C., Gorham, A. T., Pack, G. T., and Rhoads, C. P. Metabolic studies in patients with cancer of the gastro-intestinal tract. I. Plasma vitamin A levels in patients with malignant neoplastic disease, particularly of the gastro-intestinal tract. *J. Clin. Investigation* 20:749-764, 1941.
22. Ralli, E. P., Bauman, E., and Roberts, L. B. The plasma levels of vitamin A after the ingestion of standard doses: studies in normal subjects and patients with cirrhosis of the liver. *J. Clin. Investigation* 20:709-713, 1941.
23. Light, R. F., Schultz, A. S., Atkin, L., and Cracas, L. J. The excretion of vitamin B<sub>1</sub> in the urine and feces. *J. Nutrition* 16:333-341, 1938.
24. Atkin, L., Schultz, A. S., and Frey, C. N. Ultramicrodetermination of thiamine by fermentation method. *J. Biol. Chem.* 129:471-476, 1939.
25. Schultz, A. S., Atkin, L., and Frey, C. N. A fermentation test for vitamin B<sub>1</sub>. II. *J. Am. Chem. Soc.* 59:2457-2460, 1937.
26. Schöpfer, W. H. Recherches sur l'emploi possible d'un test végétal pour la vitamine B<sub>1</sub>. Essai d'étalonnage. *Bull. Soc. chim. biol.* 17:1097-1109, 1935.
27. Meiklejohn, A. P. Estimation of vitamin B<sub>1</sub> in blood by modification of Schöpfer's test. *Biochem. J.* 31:1441-1451, 1937.
28. Jansen, B. C. P. Quantitative Bestimmung von Aneurin (= Vitamin B<sub>1</sub>). *Ztschr. J. Vitaminsforsch.* 7:239-244, 1938.
29. Prebluda, H. J., and McCollum, E. V. A chemical reagent for thiamine. *J. Biol. Chem.* 127:495-503, 1939.
30. Melnick, D., and Field, H., Jr. Chemical determination, stability, and form of thiamine in urine. *J. Biol. Chem.* 130:97-107, 1939.
31. Idem. Chemical determination of vitamin B<sub>1</sub>. II. Method for estimation of the thiamine content of biological materials with the diazotized *p*-aminoacetophenone reagent. *J. Biol. Chem.* 127:515-530, 1939.
32. Egaña, E., and Meiklejohn, A. P. The estimation of thiamine in urine. *J. Biol. Chem.* 141:859-870, 1941.
33. Westenbrink, H. G. K., and Goudsmit, J. Chemical method for determination of vitamin B<sub>1</sub> in urine. *Nederl. tijdschr. v. geneesk.* 81:2632-2639, 1937.
34. Jowett, M. The estimation of vitamin B<sub>1</sub> in urine. *Biochem. J.* 34:1345-1355, 1940.
35. Rittner, K. Die Aneurinbestimmung in kleinen Blutmengen nach dem Thiochromverfahren. *Klin. Wchnschr.* 18:852-854, 1939.
36. Idem. Über die Ausscheidung von peroral und parenteral zugeführten Aneurin. *Klin. Wchnschr.* 17:1397-1400, 1938.
37. Melnick, D., Field, H., Jr., and Robinson, W. D. A quantitative chemical study of the urinary excretion of thiamine by normal individuals. *J. Nutrition* 18:593-610, 1939.
38. Dorson, H. J. Clinical application of the thiochrome reaction in the study of thiamin (vitamin B<sub>1</sub>) deficiency. *Ann. Int. Med.* 14:1-2, 1940.
39. Roskelley, R. C. Personal communication.
40. Elton, K. O'S., and Machella, T. E. Studies of the B vitamins in the human subject. I. The intake of thiamine and its relation to other dietary constituents in food selected by the normal subject. *Am. J. M. Sc.* 202:502-512, 1941. II. Urinary excretion of ingested thiamine in patients with chronic hepatic disease. *Ibid.* 202:512-516, 1941.
41. Lohmann, K., and Schuster, P. Untersuchungen über die Cocarboxylase. *Biochem. Ztschr.* 294:188-214, 1937.
42. Nachmansohn, D., and Steinbach, H. B. On the localization of enzymes in nerve fibers. *Science* 95:76, 1942.
43. Egaña, E. Personal communication.
44. Kuhn, R., György, P., and Wagner-Jauregg, T. Über eine neue Klasse von Naturfarbstoffen. *Ber. d. deutsch. chem. Gesellsch.* 66:317-320, 1933.
45. Koschura, W. Über Harnlyochrome. *Ztschr. f. physiol. Chem.* 232:101-116, 1935.
46. Najjar, V. A. The fluorimetric determination of riboflavin in urine and other biological fluids. *J. Biol. Chem.* 141:355-364, 1941.
47. Hodson, A. Z., and Norris, L. C. A fluorimetric method for determining the riboflavin content of foodstuffs. *J. Biol. Chem.* 131:621-63, 1939.
48. Ferrebee, J. W. The urinary excretion of riboflavin: fluorimetric methods for its estimation. *J. Clin. Investigation* 19:251-256, 1940.
49. Conner, R. T., and Straub, G. J. Combined determination of riboflavin and thiamin in foodstuffs. *Indust. & Engin. Chem. (Anal. Ed.)* 13:385-388, 1941.
50. Kuhn, R., and Moruzzi, G. Über die Dissoziationskonstanten der Flavine: pH-Abhängigkeit der Fluoreszenz. *Ber. d. deutsch. chem. Gesellsch.* 67B:888-891, 1934.
51. Idem. Ueber die Konstitution des Lumilactoflavins. *Ber. d. deutsch. chem. Gesellsch.* 67:888-891, 1298, 1934.
52. Henry, K. M., Houston, J., and Kon, S. K. The estimation of riboflavin. II. *Biochem. J.* 34:607-609, 1940.
53. Arnold, A., Lipsius, S. T., and Greene, D. J. Riboflavin determination by the microbiological method. *Food Research* 6:39-43, 1941.
54. Snell, E. E., and Strong, F. M. A microbiological assay for riboflavin. *Indust. & Engin. Chem. (Anal. Ed.)* 11:346-350, 1939.
55. Emmerie, A. On the relation between intake and excretion of flavin. *Acta. brev. Neerland.* 7:71, 1937.
56. Karrer, P., Erel, P., Kingier, B. H., and Bendas, H. Lactoflavin phosphorsäure-Adenin-nucleotid aus Leber und das Coferment d'-Alanin-dehydrogenase. *Helvet. chim. acta* 21:826-828, 1938.
57. Sebrell, W. H. Vitamins in relation to the prevention and treatment of pellagra. *J. A. M. A.* 110:1665-1672, 1938.
58. Klein, J. R., and Kohn, H. I. The synthesis of flavin-adenine dinucleotide from riboflavin by human blood cells in vitro and in vivo. *J. Biol. Chem.* 136:177-189, 1940.
59. Cowgill, G. R. The vitamin requirements of man. *J. Am. Dietet.* 13:195-214, 1937.
60. Stiebling, H. K., and Phipard, E. F. *Diets of Families of Employed Wage Earners and Clerical Workers in Cities.* United States Department of Agriculture Circular No. 507. 141 pp. Washington: Government Printing Office, 1939.
61. Axelrod, A. E., Spies, T. D., and Elvehjem, C. A. Riboflavin content of blood and muscle in normal and in malnourished humans. *Proc. Soc. Exper. Biol. & Med.* 46:146-149, 1941.
62. Strong, F. M., Feeney, R. E., Moore, B., and Parsons, H. T. I. Riboflavin content of blood and urine. *J. Biol. Chem.* 137:563-5, 1941.
63. Kensler, C. J., Dexter, S. O., and Rhoads, C. P. The inhibition of a di-phosphopyridine nucleotide system by split products of methylaminoozobenzene. *Cancer Research* 2:1-10, 1942.
64. Kensler, C. J., Sugiyara, K., and Rhoads, C. P. Coenzyme I and riboflavin content of livers of rats fed butter yellow. *Science* 91:6, 1940.
65. Gorham, A. T., Abels, J. C., Robins, A. L., and Rhoads, C. P. I. measurement and metabolism of thiamin and of a pyrimidine stimulating yeast fermentation found in the blood cells and urine of normal individuals. *J. Clin. Investigation* 21:161-176, 1942.
66. Abels, J. C., Gorham, A. T., Craver, L., and Rhoads, C. P. The measurement and metabolism of thiamin and of a pyrimidine stimulating yeast fermentation found in the blood cells and urine of patients with leukemia. *J. Clin. Investigation* 21:177-189, 1942.

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTE MORTEM AND POST MORTEM RECORDS AS USED  
IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, MD, *Editor*

### CASE 28161

#### PRESENTATION OF CASE

A thirty-five-year old clerical worker was admitted to the hospital because of abdominal enlargement.

Three years before entry, the patient, who had previously been quite well, began to have vague abdominal distention and sensations of epigastric illness after meals, relieved by soda. There were no other symptoms. After about two years, the distention and fullness became severer, and the patient began to lose appetite. He limited his diet to fruit and vegetables. Cough, productive of small amounts of mucoid sputum, next appeared. The patient consulted his physician, and was referred to a sanatorium. Physical examination at that time showed great enlargement of the spleen, the lower pole reaching to the level of the left iliac crest. A few moist rales were heard at the left apex. A large "hemangioma" involved the left hand, in the area of ulnar-nerve distribution. The blood showed a white cell count of 4700, with 54 per cent polymorphonuclears, 39 per cent lymphocytes, 1 per cent monocytes and 5 per cent eosinophils. The red cell count was 4,100,000, with 32 per cent hemoglobin. The icteric index was 50. The blood Hinton reaction was negative. The sputum was negative. A roentgenogram of the chest showed bilateral apical mottling, reaching to the second interspace on the right and to the third interspace on the left. A roentgenogram of the abdomen showed several large arcs of calcification in the lower portion. A roentgenogram of the left hand showed a rounded, laminated calcified nodule in the "hemangioma." A roentgenogram of the esophagus showed no evidence of varices. Two guinea pig inoculations of gastric washings were negative. The patient stayed in the sanatorium five months, and then left against advice, roentgenograms of the chest showing no regression of the mottling. A month later, he came to this hospital.

The past and family histories were irrelevant. There was no known exposure to tuberculosis. The patient had not been farther south than Washington, D. C.

On entry, the patient appeared well developed and nourished. The chest was flat, with somewhat limited expansion. Krong's isthmus was

narrowed to percussion on both sides, more on the left than on the right. No rales were heard. There was an area of increased breath sounds about 2 cm in diameter in the fourth left interspace, posteriorly. The lungs were otherwise normal. The heart was normal. The abdomen was soft, and the liver was not palpable. A large, firm, smooth mass lay in the left upper quadrant, extending halfway toward the midline and moving slightly on inspiration. There were no signs of free fluid. A soft swelling extended between the fourth and fifth fingers of the left hand, from palm to dorsum. A small, rounded, hard mass was palpable within this swelling.

The temperature, pulse and respirations were normal. The blood pressure was 100 systolic, 70 diastolic.

Examination of the blood showed a red cell count of 4,200,000 with 83 per cent hemoglobin, and a white cell count of 8000 with 79 per cent polymorphonuclears, 6 per cent lymphocytes, 14 per cent monocytes and 2 per cent basophils. No parasites were seen on smear. The red cells showed slight variation in shape. The serum protein was 9.4 gm per 100 cc, with an albumin-globulin ratio of 1.09. The nonprotein nitrogen was 20 mg. per 100 cc. The van den Bergh reaction was biphasic and slightly elevated. The urine was normal. A Congo red test showed 77 per cent retention. The tuberculin test was negative in a 1:10,000 dilution. The Frei test was negative. Gastric analysis showed 30 units of free acid half an hour after histamine.

A roentgenogram of the chest showed mottled increased density in both upper lung fields, with fine mottling in the left lower lung field. An apparent cavity was seen by fluoroscope in the right infraclavicular area. The heart was normal. The left diaphragm was slightly elevated and showed impaired motion. Roentgenograms of the upper gastrointestinal tract showed slight questionable dilatation of the folds of the lower esophagus. The otherwise normal stomach was displaced to the right by the greatly enlarged spleen. Multiple calcified mesenteric nodes were visible. Subsequent roentgenograms showed no evidence of a pulmonary cavity, and no evidence of esophageal varices.

On the seventh hospital day, peritoneoscopy was performed.

#### DIFFERENTIAL DIAGNOSIS

DR. JACOB LERMAN: May we see the x-ray films?

DR. AUBREY O. HAMPTON: There are only one or two films of the esophagus that show the slightest suggestion of varices; all the rest are normal. I do not believe that the patient had any varices.

What appears to be the spleen comes to the crest of the ilium and displaces the stomach medially. The liver is 4 cm. above the right iliac crest, but the diaphragm is low on both sides, so that it is not a huge liver. Examination of the chest shows what appears to be tuberculosis in both upper lobes. There is mottled density on both sides and old pleurisy at the left base quite characteristic of tuberculosis. The questionable cavity disappeared in further examinations. The lower lobes are normal. The pathologic lesions are all in the upper lobes. Then we have a film of the hands; there is no pulmonary osteoarthropathy. The areas of calcification in the abdomen, these large round masses varying from 1 to 3 cm., have the appearance of tuberculous lymph nodes.

DR. LERMAN: The differential diagnosis centers about three important findings: splenomegaly, pulmonary disease, as indicated by the x-ray film, and "hemangioma" of the left hand, which was probably incidental. I shall consider the causes of enlargement of the spleen under three main headings: infections, tumors and miscellaneous factors.

Under the heading of infection, one must consider tuberculosis (tuberculoma) of the spleen as most likely in this case. This would explain the pulmonary picture and the calcified nodules in the abdomen referred to by Dr. Hampton. However, the absence of wasting, fever and other systemic symptoms is against this diagnosis. The failure to detect acid-fast organisms and the negative tuberculin reaction in a dilution of 1:10,000 argue strongly against tuberculosis but do not rule it out. I do not favor this diagnosis. Syphilitic gumma of the spleen must next be considered. The irrelevant history, absence of syphilitic disease elsewhere and negative blood Hinton reaction rule it out. Chronic malaria may give such a large spleen, but there was no history of malaria, and the blood smear was negative for malarial organisms. Finally, one should mention kala-azar as the cause of a large spleen. It need not be considered in this case because the patient had never been outside this country and the blood smears were negative for leishmania organisms. Of the diagnoses so far mentioned, only kala-azar would explain the high serum protein. This last finding also raises the possibility of lymphogranuloma inguinale, in which an elevated serum protein is common. The negative Frei test practically excludes this diagnosis.

So far as the possibility of tumor is concerned, hemangioma suggests itself as the most likely benign tumor because of the presence of hemangioma elsewhere. There is nothing to corroborate this diagnosis, which does not explain the pulmonary findings. Malignant tumors such as reticulum-cell sarcoma, lymphosarcoma, lymphoma and endo-

thelioma are unlikely because of the absence of systemic symptoms and of involvement elsewhere, considering the duration of the disease. A biopsy would be necessary for an absolute diagnosis. Chronic myelogenous leukemia is a frequent cause for such a large spleen. However, the absence of systemic symptoms, of severe anemia and of abnormal cells in the blood, as well as the high serum protein, excludes this disease. A cyst of the spleen is a possibility, but the description of the character of the spleen does not fit that of a cyst.

I must consider, in passing, the possibility of multiple myeloma, which is suggested by the high serum protein. There is nothing else in the description of the case that fits this diagnosis. Also worth mentioning are Gaucher's disease, hemolytic jaundice and thrombocytopenic purpura as causes of splenomegaly. There are no findings in this case to support any of these diagnoses.

There remain three diagnoses that fit this case best: amyloid disease, Banti's syndrome and sarcoid. The first two require an additional diagnosis to explain the pulmonary findings, whereas sarcoid accounts for both the splenomegaly and the pulmonary lesions.

Amyloid disease associated with pulmonary tuberculosis or nontuberculous pulmonary infection is a strong possibility. The absence of albuminuria, the high serum protein and the normal Congo-red test fail to corroborate it but do not rule it out. The enlargement of the liver mentioned by Dr. Hampton and the elevated van den Bergh reaction suggest liver involvement consistent with amyloid disease. In the early stages of this disease, there may be a high serum protein, with increased amounts of globulin.

Under Banti's disease, or splenic-vein hypertension, I am including such conditions as portal cirrhosis with splenomegaly or splenomegaly ending in portal cirrhosis, splenic-vein thrombosis and another type of splenic-vein obstruction. The age, duration of symptoms, relative good health of the patient, slight normochromic anemia and slight leukopenia are consistent with the diagnosis. The evidence of slight liver involvement is also in favor. At times, a high serum protein with hyperglobulinemia may occur in the early stages of cirrhosis. The absence of gastric bleeding is strongly against Banti's disease. Esophageal varices have played hide-and-seek with us. The failure to find them also argues against this diagnosis. Furthermore, the presence of an associated pulmonary infection, tuberculous or nontuberculous, must be assumed, to explain the findings in the lungs.

Sarcoid would explain the large spleen, together with the signs in the lungs, although the signs are not typical. The cases that I have seen have

shown involvement around the hilar regions, with areas of increased density radiating to the lower lung fields. Moreover, the spleen is unusually large for sarcoid, which may, however, be of this size. The elevated serum protein and the hyperglobulinemia are characteristic of sarcoid. The absence of skin, lymph-node and bone involvement argues against sarcoid but does not rule it out.

Of these diagnoses, I believe sarcoid is the most likely. The other possibilities are amyloid disease and Banti's disease, associated with pulmonary tuberculosis or nontuberculous pulmonary infection.

DR. HAMPTON. I think that would be a very unusual picture for sarcoid in the chest. I do not believe that we have seen localization of the pulmonary lesion to that extent in sarcoid.

DR. LERMAN: I agree; I mentioned the fact that it is unusual for sarcoid. The lesions are usually lower and around the hilum.

DR. DONALD S. KING: Or diffuse through both lungs. We advised peritoneoscopy on this patient because he was much like the one of Dr. Robert S. Palmer's patients who was operated on for a large spleen and who had an x-ray film a good deal like this. But this lung does have lesions down toward the base.

DR. HAMPTON: A spleen as large as that in sarcoid must be rare.

DR. TRACY B. MALLORY: We have had two sarcoid spleens weighing approximately 1000 gm.

DR. LERMAN: There are cases in the literature in which splenectomy was done.

DR. KING: Dr. Palmer's case looked like milary tuberculosis. They took the spleen out at operation, thinking that it was milary tuberculosis.

DR. MALLORY: Dr. Benedict, do you want to tell about the peritoneoscopy?

DR. EDWARD B. BENEDICT: The liver showed multiple fine, gray, linear markings, and the spleen showed pin-point gray markings on the surface, high above the splenic notch. The spleen was enlarged to the umbilicus. The liver did not appear very large. This slide shows the appearance of the liver.

DR. MALLORY: I am quite sure if I saw the surface of the liver looking like that I should have no idea what it was.

DR. BENEDICT: This is the artist's interpretation, and I think it is accurate. I called Dr. Castleman to look at it, and as a matter of fact he said it was consistent with what the diagnosis was.

DR. MALLORY: That was a good guess.

#### CLINICAL DIAGNOSES

Splenomegaly and pulmonary pathology.  
Sarcoid?

#### DR. LERMAN'S DIAGNOSIS

Sarcoid

#### ANATOMICAL DIAGNOSIS

Sarcoid.

#### PATHOLOGICAL DISCUSSION

DR. MALLORY. Dr. Benedict removed a small piece of the liver, sections of which showed considerable fibrosis, but no signs of caseation; it seemed to us typical of sarcoid. We have a little further confirmatory evidence. This patient was kept on the wards some weeks without much change, allowed to go home, told to rest as much as possible and to keep on a high vitamin diet and so forth. Shortly after his return home, he developed some peculiar gastric symptoms, with almost constant nausea, and came back to the hospital again. Studies were made that offered no explanation for the symptoms. Both x-ray examination and gastroscopy were essentially negative, although I think that Dr. Benedict reported a little superficial gastritis. After a few weeks, this quieted down; the patient was again discharged and has been seen at monthly intervals up to last September. During this last period he has grown progressively better and, when last seen, expected to go back to work in a couple of days. On one entity, it was noted that he had a rather granular conjunctivitis, and a biopsy likewise showed typical sarcoid. So that we have two biopsies showing the same thing.

DR. ALFRED KRANES: Did the enlarged spleen disappear?

DR. MALLORY: There was no note on the last occasion about the spleen. It stayed large for a long time, I am sure.

DR. HAMPTON: I think that this film was taken a month later. The chest appears normal, or practically normal. It has cleared up somewhat.

DR. ALLAN M. BUTLER: Is there any comment regarding therapy for this case?

DR. KING: Symptomatic treatment is all that one can do. The disease will clear up almost always without any therapy.

#### CASE 28162

#### PRESENTATION OF CASE

A sixty-year old Swedish watchmaker was admitted to the hospital because of diarrhea.

The patient was quite well until about two years before entry, when he began to have bouts of diarrhea. Each episode lasted three or four days, during which from five to seven urgent watery movements occurred daily. The diarrhea alternated with periods of three to five days of normal bowel movements. The patient was never constipated. On occasion, the stools were foul smelling and included mucus, but no blood was

ever noted. In the first year of the illness, the patient consulted two physicians, and was given various pills and medicines. A year before entry, following an upper respiratory infection, he began to cough up small amounts of thick sputum. He had no chest pain, and the sputum contained no blood. The cough abated appreciably after several days of bed rest, but never went away entirely. At about this time, the patient became aware of a small left inguinal hernia, which persisted. In the year before entry, the diarrhea became more frequent and severer. Occasionally, movements occurred at night. In this last year, a gnawing epigastric pain also appeared, gradually becoming worse. This pain was sometimes accompanied by cramping pain in the lower abdomen, followed by an episode of diarrhea. Occasionally, food relieved the epigastric pain, but otherwise there was no relation between the pain and meals. At times, the pain came on at night, when it radiated to the lumbar region. Throughout the illness, there was insidious progression of weakness and fatigability, and a loss of 36 pounds in weight.

On admission, the patient appeared large, powerfully built, fairly well nourished and in no acute distress. The skin was pale. The axillary and inguinal lymph nodes were shotty. The lungs were clear. The heart was not remarkable. The abdomen showed diastasis of the rectus muscles in the epigastric region. An indefinite, firm, tennis-ball-sized mass was palpable in the right upper quadrant, moving on respiration. A small, reducible indirect hernia was present in the left inguinal region. A firm, moderately hypertrophied prostate was palpable by rectum.

The blood pressure, pulse, temperature and respirations were normal.

Examination of the blood showed a red-cell count of 3,800,000 with 8.5 gm. hemoglobin, and a white-cell count of 18,300 with 66 per cent polymorphonuclears. The urine showed a trace of sugar. The stools were liquid brown and guaiac negative. Stool culture was negative for pathogens. The serum protein was 4.9 gm. per 100 cc.

Roentgenograms of the large bowel showed a ready flow of barium through the rectum and sigmoid to a point in the midtransverse colon beyond which the barium would not pass. At this level, there was a constant filling defect, with a scalloped, irregular polypoid margin. The folds of the mucosa appeared markedly thickened for a distance of 5 cm. beyond this place. In another examination, barium flowed readily through the sigmoid and transverse colon to outline a cone-shaped narrowing in the region of the hepatic flexure. There were two nodular filling defects at the proximal end of the area of obstruction.

Apparent mucosal markings remained in the area of narrowing, arranged in concentric rings at the distal widest point. A roentgenogram of the chest showed no evidence of disease.

On the tenth hospital day, an operation was performed.

#### DIFFERENTIAL DIAGNOSIS

DR. ALLEN G. BRAILEY: This history presents a classic example of slowly developing obstruction of the large bowel. The exact mechanism of such recurrent bouts of diarrhea is not known but it is likely that the irritation of the obstructing lesion, in addition to the irritation of fecal material behind the obstruction, produces an increase of tonus of the muscular wall and more and more vigorous peristalsis, until finally the obstruction is overcome. The abnormally vigorous peristalsis then results in diarrhea, just as it does when produced by any other cause. After the bowel is emptied, a period of rest ensues until the accumulated bowel contents start the cycle over again. The bouts of diarrhea occurred at ever-shortening intervals, and the muscular activity of the bowel proximal to the obstruction became more and more vigorous until actual colicky pain appeared. Nothing is said about loss of appetite, but we know that such an interference with normal intestinal motility invariably results in anorexia, and this is borne out by the fact that the patient was reported to have lost 36 pounds in weight. The malnutrition that resulted from the anorexia probably accounted for his weakness and fatigability, his anemia and his lowered serum protein, although there may have been other causes for these impairments of health.

This train of events was set off by an obstructive lesion of the midtransverse colon whose x-ray description is somewhat unusual. Have you anything further to say about that, Dr. Hampton?

DR. AUBREY O. HAMPTON: I remember the film very well, and I know the answer. The conical defect with multiple small, round, filling defects in the transverse colon was definitely unusual. We did not demonstrate the whole lesion, because we could not get barium beyond the point of obstruction, but the distal margin did not show the usual picture of carcinoma. It had too many fine, irregular projections from it.

DR. BRAILEY: Was there evidence of polyps anywhere else?

DR. HAMPTON: There were no other polyps. These polyp-appearing things were all grouped together in one spot, but we could not tell whether they were continuous or not.

DR. BRAILEY: Do you think that the mucosa was normal? It was not destroyed?

DR. HAMPTON: In the area near the polypoid

fects, it was normal, but toward the obstruction it was lost in a mass of polypoid defects.

DR. BRAILEY: Our first problem is to decide whether this was a lesion that began in the mucosa or whether it was intramural in origin. The statement is made that "the stools were liquid brown and guaiac negative." If the stools were persistently guaiac negative, they provide evidence of great importance in deciding the nature of this lesion. How many stools were examined?

DR. TRACY B. MALLORY: One stool was examined. The other stool was cultured but not tested for guaiac.

DR. BRAILEY: That is too bad. I presume one might have an occasional stool with a negative guaiac reaction, but certainly it is very rare in carcinoma that has developed to the point of obstruction. The mucosa is destroyed, and oozing must occur.

I assume that this observation can be trusted, and we can therefore exclude practically any lesion, such as carcinoma, that arose in the mucosa or destroyed the mucosa, for all such lesions ooze blood and most if not all the stools would show the presence of occult blood. If I do not lose my courage and am consistent with this line of reasoning, the lesion developed within the wall of the bowel. It might have been tuberculosis. Although the x-ray appearance was not very suggestive of tuberculosis, I do not believe that this rules it out. On the other hand, tuberculosis almost invariably involves the mucosa with ulceration at an early stage; it very rarely develops in a man of this age who has no evidence of tuberculosis in the chest, and I therefore discard tuberculosis as a likely possibility. I believe that it is much more probable that this man had a new growth as the cause of his obstruction. If we must exclude primary carcinoma for lack of bleeding, we are left with metastatic tumor, which is too unlikely to be considered further, and with the various sarcomas that may develop from bowel-wall structures. These include leiomyosarcoma, angiosarcoma, sarcomas arising from nerve tissue and various types of lymphoblastoma. It is obvious that this man required an operation. It is also clear that a final diagnosis could not be made without pathological study. However, I think that lymphosarcoma is the best bet.

DR. CHESTER M. JONES: I should like to disagree with Dr. Brailey. We have been surprised at the number of patients with carcinoma of the stomach and bowel who for days on end have had guaiac-negative stools. No diagnostic inference can be placed on that, even if it were correct. Dr. Hampton points out that the relatively low red-cell count suggests that the stool report was

not correct. Even if the anemia were based on malnutrition, it does not to my mind rule out cancer in any way.

It is a bit interesting to know the cause of the epigastric pain. The patient had two sets of symptoms. One set appeared quite late, and one had persisted for two years.

DR. WYMAN RICHARDSON: May I add to that statement the fact that the patient had not only a red-cell count of 3,800,000 but a hemoglobin of 8.5 gm. This means that he had a very severe hypochromic anemia, which further means he had lost blood from his bowel no matter whether the stools were guaiac negative or not. There is no question that this lesion had been bleeding—if these figures are correct, I hasten to add.

DR. BRAILEY: I started out with the assumption that there was no bleeding, but certainly with only one stool recorded I cannot maintain that argument. If we concede the bleeding, I should put my money on carcinoma rather than anything else.

DR. HAMPTON: We presented the case in our conference; I have forgotten the whole discussion, but I do not remember seeing a carcinoma with obstruction of this appearance, with these multiple, small, rounded defects as though there were many polyps in one place in the bowel—a picture of local polyposis, which I have never heard of, and at the same time a conical obstruction instead of a transverse, circular one. I do not know what our conclusions were, but I am interested in knowing what the histology is going to be.

DR. MALLORY: On the x-ray report, it was stated, "Probably carcinoma, but might well be lymphoma."

DR. HAMPTON: I think we hedged quite a bit; I should do so.

DR. JACOB LERMAN: Was there no comment about the mass that moved on respiration? If it was in the colon, it certainly would not move on respiration.

DR. HAMPTON: I disagree—the colon does move with respiration.

DR. BRAILEY: I am interested in Dr. Jones's comment that in frankly ulcerative carcinoma one can have repeated stools without blood in them.

DR. JONES: I did not say exactly that. I said that patients with cancer of the stomach or intestine—not, frankly ulcerative cancer—may go from days to weeks with no blood in the stools.

DR. BRAILEY: When the lesion is large enough to obstruct the bowel?

DR. JONES: I should not hedge on it a bit.



DR. CLAUDE E. WELCH: The Medical Department told us that this man had cancer of the colon. We did not see any reason to doubt the diagnosis and operated, with a two-stage resection. At the time of the ileocolostomy, a huge mass was located directly over the duodenum. The patient survived the first stage, and about two weeks later a resection was done. At that time, we observed considerable fixation of the mass posteriorly. It was hoped that this might turn out to be inflammatory. By the end of the resection, however, it was evident that there was considerable extension of the disease into the pancreas and that the wall of the duodenum was involved; a few nodules were found on the stomach. The main mass was taken out, but we knew we had left tumor behind.

#### CLINICAL DIAGNOSIS

Carcinoma of colon.

#### DR. BRAILEY'S DIAGNOSIS

Lymphosarcoma of colon.

#### ANATOMICAL DIAGNOSIS

Carcinoma of colon.

#### PATHOLOGICAL DISCUSSION

DR. MALLORY: The specimen showed a very extensive carcinoma of quite low-grade malignancy. It involved 12 cm. of the bowel. Above the mass, the mucosa was very markedly edematous,—in fact, in some places more than 1.5 cm. in thickness,—but that could not explain the x-ray findings because the radiologists never saw the proximal side of the lesion. There were numerous polypoid tumor excrescences along the distal margin of the tumor, which I suppose they saw.

DR. HAMPTON: I saw the specimen, and I thought there were some fairly long mosslike strands of carcinoma protruding from the margins that probably floated in the barium.

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established in 1828

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND  
PUBLISHED UNDER THE JURISDICTION OF THE  
COMMITTEE ON PUBLICATIONS

Official Organ of

THE MASSACHUSETTS MEDICAL SOCIETY  
and

THE NEW HAMPSHIRE MEDICAL SOCIETY

## EDITORIAL BOARD

Joseph Garland M D	Stephen Rushmore M D
William B Breed M D	Henry R Viets M D
George R Minot, M D	Robert M Green M D
Frank H Lahey M D	Charles C Lund M D
Swelda Warren M D	John F Fulton M D
George L. Tobey, Jr, M D	A. Warren Stearns M D
C. Guy Lane M D	Dwight O Hara M D
William A Rogers M D	Chester S Keeler M D

## ASSOCIATE EDITORS

Thomas H Lanman M D	Donald Munro M D
Henry Jackson Jr M D	

Walter P Bowers M D, EDITOR EMERITUS  
Robert N Nye M D, MANAGING EDITOR  
Clara D Davies, ASSISTANT EDITOR

SUBSCRIPTION TERMS \$600 per year in advance postage paid for the United States (medical students \$350 per year), Canada \$7.04 per year. Non funds \$3.52 per year for all foreign countries belonging to the Postal Union.

MATERIAL for early publication should be received not later than noon Friday.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine* 8 Fenway Boston Massachusetts.

## ELECTEES AND THEIR PHYSICAL FITNESS

The successful waging of any war depends on many factors. One of the more important is the physical fitness of the combat personnel. Much has been said concerning the health of the young men of this country, and there seems to be a rather general belief that they are strong and healthy. It has been claimed that the United States is a nation of athletes. But to be athletic does not necessarily imply that one can come up to the physical standards of the Army of the United States or the United States Navy. One well known professional football player was recently rejected by the Army for malignant hypertension. Furthermore,

two decades ago, a noted collegiate football player successfully represented one of the large universities for four years, even though he was known to have a high grade mitral stenosis, which was proved at autopsy a few years later. In the same era, one of the country's most renowned fencers had had infantile paralysis in early childhood.

Adequate and authoritative figures concerning the health of the Nation so far as the armed forces are concerned have heretofore been difficult to obtain, and it should be remembered that a really true picture can be had only from the collective data obtained from the selective service boards, the Army induction centers and the certificates of disability discharge after induction, with the exception, of course, of those discharges due to injuries in line of duty.

A preliminary survey<sup>1</sup> covering the first two types of examination is now at hand. It is illuminating but not encouraging. Fifty per cent of the approximately 2,000,000 registrants who were examined prior to May 31, 1941, were found unqualified for general military service by selective-service boards and Army induction centers because of physical, mental or educational defects or a combination of these. Twenty five per cent were considered unsuitable for any type of military service. The requirements for the Army and Navy are rigid, but certainly not unduly so. That roughly half our young men should be unsuited for military service does not reflect too well on the state of health of the Nation, and it should be remembered that this survey took no account of the hundreds of discharges for physical or mental handicaps that were missed during the preliminary examinations and that came to light only after a few weeks or months in camp.

Nor does one gain much solace from the breakdown of the figures. "Based on the major defect or principal cause of rejection, dental defects account for . . . 20.9 per cent of the 900,000 registrants not qualified for general military service . . ." It is probable—indeed almost certain

DR. CLAUDE E. WELCH: The Medical Department told us that this man had cancer of the colon. We did not see any reason to doubt the diagnosis and operated, with a two-stage resection. At the time of the ileocolostomy, a huge mass was located directly over the duodenum. The patient survived the first stage, and about two weeks later a resection was done. At that time, we observed considerable fixation of the mass posteriorly. It was hoped that this might turn out to be inflammatory. By the end of the resection, however, it was evident that there was considerable extension of the disease into the pancreas and that the wall of the duodenum was involved; a few nodules were found on the stomach. The main mass was taken out, but we knew we had left tumor behind.

#### CLINICAL DIAGNOSIS

Carcinoma of colon.

#### DR. BRAILEY'S DIAGNOSIS

Lymphosarcoma of colon.

#### ANATOMICAL DIAGNOSIS

Carcinoma of colon.

#### PATHOLOGICAL DISCUSSION

DR. MALLORY: The specimen showed a very extensive carcinoma of quite low-grade malignancy. It involved 12 cm. of the bowel. Above the mass, the mucosa was very markedly edematous,—in fact, in some places more than 1.5 cm. in thickness,—but that could not explain the x-ray findings because the radiologists never saw the proximal side of the lesion. There were numerous polypoid tumor excrescences along the distal margin of the tumor, which I suppose they saw.

DR. HAMPTON: I saw the specimen, and I thought there were some fairly long mosslike strands of carcinoma protruding from the margins that probably floated in the barium.

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established in 1828

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND  
PUBLISHED UNDER THE JURISDICTION OF THE  
COMMITTEE ON PUBLICATIONS

Official Organ of  
THE MASSACHUSETTS MEDICAL SOCIETY  
and  
THE NEW HAMPSHIRE MEDICAL SOCIETY

## EDITORIAL BOARD

Joseph Garland, M.D.	Stephen Rushmore, M.D.
William B. Breed, M.D.	Henry R. Viets, M.D.
George R. Minot, M.D.	Robert M. Green, M.D.
Frank H. Lacey, M.D.	Charles C. Lund, M.D.
Shields Warren, M.D.	John F. Fulton, M.D.
George L. Tobey, Jr., M.D.	A. Warren Stearns, M.D.
C. Guy Lane, M.D.	Dwight O'Hara, M.D.
William A. Rogers, M.D.	Chester S. Keefer, M.D.

## ASSOCIATE EDITORS

Thomas H. Lenzon, M.D.	Donald Munro, M.D.
Henry Jackson, Jr., M.D.	

Walter F. Bowers, M.D., EDITOR EMERITUS  
Robert N. Nye, M.D., MANAGING EDITOR  
Clara D. Davies, ASSISTANT EDITOR

**SUBSCRIPTION TERMS:** \$6.00 per year in advance, postage paid, for the United States (medical students, \$3.50 per year); Canada, \$7.04 per year, foreign funds; \$8.52 per year for all foreign countries belonging to the postal Union.

**MATERIAL** for early publication should be received not later than noon on Friday.

The Journal does not hold itself responsible for statements made by any contributor.

**COMMUNICATIONS** should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston, Massachusetts.

## SELECTEES AND THEIR PHYSICAL FITNESS

THE successful waging of any war depends on many factors. One of the more important is the physical fitness of the combat personnel. Much has been said concerning the health of the young men of this country, and there seems to be a rather general belief that they are strong and healthy. It has been claimed that the United States is a nation of athletes. But to be athletic does not necessarily imply that one can come up to the physical standards of the Army of the United States or the United States Navy. One well-known professional football player was recently rejected by the Army for malignant hypertension. Furthermore,

two decades ago, a noted collegiate football player successfully represented one of the large universities for four years, even though he was known to have a high-grade mitral stenosis, which was proved at autopsy a few years later. In the same era, one of the country's most renowned fencers had had infantile paralysis in early childhood.

Adequate and authoritative figures concerning the health of the Nation so far as the armed forces are concerned have heretofore been difficult to obtain, and it should be remembered that a really true picture can be had only from the collective data obtained from the selective-service boards, the Army induction centers and the certificates of disability discharge after induction, with the exception, of course, of those discharges due to injuries in line of duty.

A preliminary survey<sup>1</sup> covering the first two types of examination is now at hand. It is illuminating but not encouraging. Fifty per cent of the approximately 2,000,000 registrants who were examined prior to May 31, 1941, were found unqualified for general military service by selective-service boards and Army induction centers because of physical, mental or educational defects or a combination of these. Twenty-five per cent were considered unsuitable for any type of military service. The requirements for the Army and Navy are rigid, but certainly not unduly so. That roughly half our young men should be unsuited for military service does not reflect too well on the state of health of the Nation, and it should be remembered that this survey took no account of the hundreds of discharges for physical or mental handicaps that were missed during the preliminary examinations and that came to light only after a few weeks or months in camp.

Nor does one gain much solace from the breakdown of the figures. "Based on the major defect or principal cause of rejection, dental defects account for . . . 20.9 per cent of the 900,000 registrants not qualified for general military service. . . ." It is probable—indeed almost certain

—that nearly all such defects can be remedied or could have been prevented; furthermore, it should be noted that these official figures do not substantiate a claim made before the Massachusetts Dental Society<sup>2</sup> that but 2 per cent of the registrants were not accepted because of dental defects. Next in order as causes for rejection came defects of the eyes and diseases of the cardiovascular system,—13 and 10 per cent, respectively,—and it is not likely that many of these disorders are remediable or were preventable. Then follow musculoskeletal defects, venereal diseases, mental or nervous disorders, hernias and defects of the ears and feet, each roughly 5 per cent. Diseases of the lungs, including tuberculosis, were a cause for rejection in but 2.9 per cent—a creditable figure, although it should be remembered that registrants of some states had no x-ray films taken prior to induction.

Exactly how many of these rejected men can be rehabilitated is impossible to say. The survey states, "Of the 900,000 who have been classed as available for limited military service or disqualified for military service, an estimated 200,000 can be completely physically rehabilitated for the performance of general military service." The President has charged the Selective Service System with such a rehabilitation program. It should be noted, however, that no provision has yet been made whereby the man enlisting can have remediable defects corrected if he voluntarily does not have the money to do so himself.

Three things seem clear: an appallingly large number of young men are unfit for military service; many of the nonremediable disqualifying defects could have been prevented; and rehabilitation should benefit not only the armed forces but the Nation as a whole—whether at peace or at war. It is to be hoped that the physicians, dentists and hospitals of this country will aid in the correction of these defects.

#### REFERENCES

1. Analysis of reports of physical examination: summary of data from 19,923 reports of physical examination. Medical Statistics Bulletin No. 1. National Headquarters, Selective Service System. Washington, D. C. November 10, 1941.
2. *Boston Herald* (February 4, 1942; page 17).

## AMERICAN INSTITUTE FOR PSYCHOANALYSIS

ORTHODOXY and the scientific attitude can scarcely be considered compatible. Earnestness in the desire to seek the truth and willingness to discard supposed facts when they cannot be substantiated must be the foundation for honest, progressive scientific work. A justifiable criticism of some psychoanalysts of the Freudian school or of some of the psychoanalytic societies is that they insist on the orthodoxy, the incontrovertible correctness, of Freud's fundamental concepts. Their zeal in supporting their master's teachings sometimes exceeds what Freud himself probably would have thought permissible. If a theory or a hypothesis is sound, it may be examined searchingly without danger to its validity and without embarrassment to its proponents. When the advocate of any thesis reacts antagonistically to a questioning analysis of the soundness of his doctrine, it is fair to doubt his fitness for scientific investigation.

Whether for personal reasons or because of an impersonal, objective interest in liberal, scientific progress, a number of the members of the New York Psychoanalytic Society last spring severed themselves from the society and established the American Institute for Psychoanalysis. According to a statement issued by them, they could no longer put up with what they termed the "dogmatism" of certain elements within the society, and they believed that the future of psychoanalysis and psychoanalytic education would be jeopardized if directed with an ex-cathedra attitude.

In the organization of the new institute, the plan is to teach psychoanalysis as "a young science, still in an experimental stage of its development, full of uncertainties, full of problems to which anything approaching final and conclusive answers is still to be sought."

The disagreements and wrangling within a particular society may be considered inevitable and healthy for the vitality of the organization. The schism here referred to may be of no general importance. Since it is well known, however, that there is a tendency in some psychoanalytic circles

to defend some of Freud's hypotheses with a bias of almost religious faith, it is well for the future of psychoanalysis if some of Freud's followers have enquiring minds. No really great teacher in medicine ever wanted investigation to go forward with the provision that the soundness of his own contributions was to remain eternally indisputable.

Freud was a man, not a deity, and he allowed himself the privilege of changing his mind. A relief that his observations and conclusions were unswervingly accurate denies human fallibility. Even in the scientific world, the power and influence of personality can be tremendous. Most men admire the attributes of leadership and superior intellect, and for many physicians who cannot accept the tenets of a theological system, the human need for security is somewhat satisfied if they think that they see ultimate truth in a supposedly scientific cloak. Combine this admiration and this need with suggestibility, which is present in all of us to more or less degree, and the critical faculty is not likely to be dominant. It is good to see that dissidence, even though possibly arising from personal resentment, may begin to break the spell of Freud's personality.

## MEDICAL EPONYM

### NIEMANN-PICK DISEASE

"Ein unbekanntes Krankheitsbild [An Unrecognized Syndrome]" was described by Dr. Albert Niemann (1880), assistant in the Berlin pediatric clinic of Professor Czerny, in the *Jahrbuch für Kinderheilkunde* (79: 1-10, 1914). A portion of the translation follows:

It is my present desire to direct the attention of my colleagues, particularly the pediatricists, to a very remarkable syndrome, which I speak of as unrecognized not only because I myself have never seen it before, but also because I have looked in vain throughout the literature for a description of it. . . .

The victim of the disease was a female child, aged seventeen months . . . who had been sick from the beginning of the second month of her life and whose chief symptom, even at that time, had apparently been a tumor, presumably of the spleen. . . .

We found a wretchedly nourished child, apathetic, underdeveloped, with wide-open fontanelles, unable to stand or walk. . . . The most striking finding on inspection was the tremendously enlarged abdomen (circumference, 50 cm.). This huge swelling consisted

of liver and spleen. The spleen extended far below the navel, as did the liver, the lower border of which was a fingerbreadth above the right anterior superior spine. The veins of the belly were markedly dilated, there was some demonstrable free fluid in the abdomen, and there were signs of congestion elsewhere: a catarrhal condition of the lungs, edema of the feet and eyelids. . . . There was no jaundice. . . . The congestive phenomena increased, diarrhea supervened, and finally after a stay of four weeks in the clinic, exitus occurred. . . .

Autopsy showed . . . a very large spleen, not excessively hard, with a rather spotted surface. Section revealed yellowish white foci, the size of a lentil, frequently confluent, between which only very narrow bands of normal splenic substance persisted, so that the cut surface looked whitish yellow when seen from a distance. . . . The liver was likewise markedly enlarged, with the color and markings of fatty degeneration such as that seen in cases of phosphorus poisoning. . . . The abdominal lymph nodes were not only moderately enlarged, but also showed a peculiar yellow fatlike color and were rather soft in consistence. . . .

Microscopic examination of the spleen showed . . . almost the whole structure to be replaced by peculiar cells . . . very large, irregular in shape, irregularly distributed, sometimes crowded together, sometimes separated from each other. They contained a small, round nucleus. . . . Exactly similar cells were found in the liver . . . and . . . also in the abdominal lymph nodes. . . . I should like to propose the name *groszzellige Drüsenmetamorphose* [large-cell glandular metamorphosis] for this disease.

Ludwig Pick (1868), director of the Pathological Anatomical Department of the Municipal Hospital, Friedrichsheim, Berlin, presented a communication, "Zur pathologischen Anatomie des Morbus Gaucher [On the Pathological Anatomy of Gaucher's Disease]," before the *Berliner medizinische Gesellschaft* on October 11, 1922. His remarks and the discussion that followed appear in the *Medizinische Klinik* (18: 1423 and 1449, 1922). A portion of the translation follows:

In a case of splenomegaly and hepatomegaly in a seventeen-month-old female child, described by Niemann in 1914 under the title "An Unrecognized Syndrome," the enlargement of the organs was due to an infiltration of lipid (phosphatid)-bearing cells, as Pick was able to show on subsequent examination of Niemann's material. This case, together with similar observations reported by Siegmund and American authors (Knox, Wahl and Schmeisser) belongs in a special group of lipid-cell splenohepatomegaly in children, in which the lipid cells are found in a considerable number of other organs (heart, dura, kidneys and so forth).

An exhaustive critique of the subject is given by Pick under the title "Der Morbus Gaucher und die ihm ähnlichen Erkrankungen [Gaucher's Disease and Similar Maladies]" in *Ergebnisse der inneren Medizin und Kinderheilkunde* (29: 519-627, 1926).

R. W. B.

## MASSACHUSETTS MEDICAL SOCIETY

## COMMITTEE ON MATERNAL WELFARE

## CASE HISTORY: ACUTE INVERSION OF THE UTERUS, CAUSING HEMORRHAGE AND DEATH

A thirty-year-old multipara had had adequate prenatal care and was delivered at term of a living child. Labor, which had been induced for reasons not stated, lasted eleven hours and forty minutes. The delivery was a breech and was said to have offered no difficulty. The condition of the mother following delivery was satisfactory. The placenta was not delivered immediately, and Credé's method was resorted to, with the result that the uterus became acutely inverted. The placenta was peeled from the uterine wall. The bleeding was tremendous, and the patient's condition became grave. A tourniquet was placed about the inverted portion of the uterus, and the patient was given 750 cc. of whole blood. In spite of this, she died before the uterus had been replaced.

*Comment.* Inversion of the uterus is always a very serious complication. In this case, it was undoubtedly induced by undue attempts at Credé's method. That the placenta was still attached when the uterus became inverted is evidence that no separation had occurred before the procedure was attempted. Such attempts should never be made until there is evidence that the placenta has separated. Had this placenta been left, it is quite probable that it would have separated spontaneously and delivered itself without undue loss of blood. It is also probable that had this uterus been replaced under anesthesia as soon as it appeared at the vulva, the subsequent hemorrhage might have been averted. It is often impossible, however, to replace an inverted uterus manually. In such a case, laparotomy is indicated.

Cases of chronic inversion of the uterus are extremely rare, since most patients with uteri that become inverted and are not replaced die of hemorrhage. However, chronic inversion has been known to exist for months. For example, when one patient who had had several hemorrhages after delivery was finally seen in consultation about three months after her baby was born, a diagnosis of chronic inversion was made. She was operated on, the uterus was replaced, and the patient has since had a living child.

The fatality in the case presented seems to have been avoidable.

## "PROBLEMS OF TUBERCULOSIS UNDER WARTIME CONDITIONS"\*

Although tuberculosis is not popularly identified as one of the four horsemen of the Apocalypse, it is unquestionably one of the major pestilences of war; there is no more sensitive barometer of national privation and suffering. In World War I, the tuberculosis mortality in all combatant countries rose within the first year and climbed steadily until after the armistice. In France, England and Germany, the rates practically doubled, and even in this country the mortality in 1918 was 50 per cent higher than that in the preceding few years. In the United States, the total deaths from tuberculosis at least equaled the losses in battle in any year of the war.

Incomplete reports from Europe show that tuberculosis had again definitely increased in 1940, and preliminary data here indicate that nearly half the states experienced a slight rise in mortality in 1941. With the prospect of a war longer, more inclusive and far more exhausting than the last, it is high time that we define the problems of tuberculosis under wartime conditions and organize all available control measures in the civilian population as well as in the armed forces.

Essentially, the problems of control are the same in war and in peace: early recognition of cases, prompt hospitalization of those needing treatment, examination of family contacts, maintenance of adequate nutrition, good housing and a reasonable sense of security. The great problem is how to attain a semblance of such conditions with restricted food supplies in a situation that calls for the expenditure of the utmost effort of which we are capable.

The first line of defense is the maintenance, at all costs, of the very effective control organization that has been built up in the last forty years. Although our sanatoriums and clinics have not been the only factors responsible for the decline of 80 per cent in the tuberculosis mortality in that period, they are the most effective weapons we possess for checking any upsurge of the insidious enemy. Prevention, far more than treatment, has been responsible for the gains that have been made, and so long as we prevent the spread of infection from open cases we shall be able to check the infiltration of our population that results in ultimate disaster.

At the beginning of the present war, the English promptly discharged to their homes a large number of patients in tuberculosis sanatoriums to make room for expected military casualties. When it was found that the beds were not needed, these tuberculosis cases were gradually returned to their hospitals, but the tuberculosis service was seriously disrupted and the damage that resulted from returning a large number of patients with contagious lesions to their homes and communities is hard to estimate. It is to be hoped that we profit by our neighbor's experience and retain, so far as possible, the exceptionally adequate sanatorium system we have built up.

Recruitment of physicians and nurses for military needs is bound to throw additional burdens on local boards of health, which have the primary legal responsibility for tuberculosis control. It is essential that reporting of cases be prompt and complete and where every doctor's load has been doubled he must depend more and more on the local public-health nurse for the follow-up and instruction of tuberculosis patients and their families that are so vital a part of prevention. When the patient has gone

\*A "Green Lights to Health" broadcast given through Station WAAB by Dr. Alton S. Pope on Saturday, February 7, and sponsored by the Public Education Committee of the Massachusetts Medical Society and the Massachusetts Department of Public Health.

o the sanatorium, it is often the nurse's responsibility to see that the other members of the family come in for x-ray examination, and when necessary, receive adequate aid during the sickness of the wage earner.

Nutrition is perhaps the most vital factor in tuberculosis control in wartime. In the last war, the tuberculosis mortality was in general proportional to the inadequacy of the food supply, and in the neutral countries a rise became noticeable only when meat and dairy products had been depleted by combatant neighbors. Nutrition has always played an important part in the treatment of tuberculosis and there is every reason to believe it can play an equally significant role in prevention. A striking example of the correlation between nutrition and tuberculosis mortality is the situation in Germany twenty years ago. Three years after the armistice, the mortality had fallen nearly to prewar levels, but in the economic collapse of 1922-1923 the food shortage became almost as acute as it had been in 1918 and the tuberculosis mortality promptly rose about 50 per cent.

During the recent depression in the United States, tuberculosis experts freely predicted a general rise in the incidence of the disease, which to date has not materialized. The most reasonable answer seems to be that in spite of the great reduction of income for most of our population, the people on relief were on the whole more adequately fed than they had been during some periods of plenty. In other words malnutrition to be a factor in the activation of tuberculosis must apparently reach a certain critical level and if we can prevent its reaching that point by proper husbanding of our supplies and by judicious planning of our diets there is reason to hope that we can minimize one of the hazards that has seemed an inevitable part of war.

In no field of social welfare has this country been backward as in housing and it is doubtful whether any social factor more seriously complicates tuberculosis control under war conditions. The spread of tuberculosis depends on two things: the transmission of the causative organism, and the resistance of the human host. Obviously, the closer the contact between the open case and a susceptible host, the more rapidly will the disease spread and no factor is more favorable to such rapid transfer than overcrowding in poorly lighted and inadequately ventilated tenements. It is of course too late to correct such a situation in the face of more pressing demands, but we can at least make every effort to discover active cases of tuberculosis and remove them to a safer environment.

Difficult as it is to maintain the existing facilities for the prevention and treatment of tuberculosis under wartime conditions, those very conditions open certain new avenues of attack. First among them has been the opportunity to secure preinduction x-ray examinations of practically all men entering the armed forces of the country. Because the Army Medical Corps was not prepared to undertake these examinations in Massachusetts when the Selective Service Act went into effect in the fall of 1940, the State Department of Public Health took on the task through its field clinic unit by means of portable x-ray apparatus. Films were furnished by the Army and exposed and interpreted by the clinic staff. In the course of a year 10,000 members of the Massachusetts National Guard and 23,000 selectees were x-rayed and 134 cases of significant tuberculosis were found, an incidence of approximately 0.5 per cent. With the institution of its own apparatus this work has now been taken over by the Army Medical Corps and the preliminary screening of

all recruits promises to reduce substantially the future needs for treatment and compensation of soldiers disabled by tuberculosis—an expense that has reached a cumulative total of nearly \$1,000,000,000 since the last war.

Treatment for recruits found to have tuberculosis is fortunately immediately available in Massachusetts. Some, however, who are disqualified by a history of tuberculosis or inactive lesions offer a real problem in rehabilitation. The New England Rehabilitation Center at Rutland has limited facilities for the training and placement of suitable candidates, but a problem remains that is a real challenge to boards of health and especially to voluntary tuberculosis associations.

The staggering demands made on industry for munitions equipment and supplies of every description have made employers receptive to procedures that promise to improve the health and efficiency of their workers and thereby reduce the labor turnover. In the textile, boot and shoe, and some other industries it has been possible to make arrangements for mass x-raying of certain groups of employees for tuberculosis case finding. Consent of the workers has been obtained through their labor unions, and reports of the findings are given to the employees only. In the groups examined, the incidence of tuberculosis has not been high,—1.5 per cent, including healed cases,—but the active cases found are at a stage favorable for treatment and a certain number of foci of infection can be removed from the factories. Even more encouraging has been the arrangement by a few firms for the pre-employment x-ray examination of their own employees. It is quite possible that such control measures which have proved their value under the pressure of wartime production, will be accepted as an essential part of our program for the elimination of tuberculosis when a return to normal living has again made that aim a rational objective.

## DEATHS

DIEZ—M. LUISE DIEZ, M.D., of Boston, died April 12. She was in her sixty-fourth year.

Dr. Diez received her degree from the Woman's Medical College of Pennsylvania in 1903. Since 1929, she was director of the Division of Child Hygiene of the Massachusetts Department of Public Health. Dr. Diez was a member of the executive committee of the Massachusetts Child Council and of the Committee on Maternal Welfare of the Massachusetts Medical Society, a fellow of the American Public Health Association and a lecturer on child hygiene at the Harvard School of Public Health. She was a member of the Massachusetts Medical Society and the American Medical Association.

GALVIN—WILLIAM GALVIN, M.D., of North Adams, died April 8. He was in his eighty-fourth year.

A native of Troy, New York, Dr. Galvin received his degree from the University of Vermont College of Medicine in 1892. He was a fellow of the Massachusetts Medical Society and the American Medical Association.

He is survived by a niece.

## WAR ACTIVITIES

DECONTAMINATION OF FATS AFTER EXPOSURE TO LEWISITE AND MUSTARD GAS

Since publication of the Office of Civilian Defense handbook *First Aid in the Prevention and Treatment of Chemical Casualties and Protection Against Gas*, further



## MASSACHUSETTS MEDICAL SOCIETY

## COMMITTEE ON MATERNAL WELFARE

## CASE HISTORY: ACUTE INVERSION OF THE UTERUS, CAUSING HEMORRHAGE AND DEATH

A thirty-year-old multipara had had adequate prenatal care and was delivered at term of a living child. Labor, which had been induced for reasons not stated, lasted eleven hours and forty minutes. The delivery was a breech and was said to have offered no difficulty. The condition of the mother following delivery was satisfactory. The placenta was not delivered immediately, and Credé's method was resorted to, with the result that the uterus became acutely inverted. The placenta was peeled from the uterine wall. The bleeding was tremendous, and the patient's condition became grave. A tourniquet was placed about the inverted portion of the uterus, and the patient was given 750 cc. of whole blood. In spite of this, she died before the uterus had been replaced.

*Comment.* Inversion of the uterus is always a very serious complication. In this case, it was undoubtedly induced by undue attempts at Credé's method. That the placenta was still attached when the uterus became inverted is evidence that no separation had occurred before the procedure was attempted. Such attempts should never be made until there is evidence that the placenta has separated. Had this placenta been left, it is quite probable that it would have separated spontaneously and delivered itself without undue loss of blood. It is also probable that had this uterus been replaced under anesthesia as soon as it appeared at the vulva, the subsequent hemorrhage might have been averted. It is often impossible, however, to replace an inverted uterus manually. In such a case, laparotomy is indicated.

Cases of chronic inversion of the uterus are extremely rare, since most patients with uteri that become inverted and are not replaced die of hemorrhage. However, chronic inversion has been known to exist for months. For example, when one patient who had had several hemorrhages after delivery was finally seen in consultation about three months after her baby was born, a diagnosis of chronic inversion was made. She was operated on, the uterus was replaced, and the patient has since had a living child.

The fatality in the case presented seems to have been avoidable.

## "PROBLEMS OF TUBERCULOSIS UNDER WARTIME CONDITIONS"

Although tuberculosis is not popularly identified as one of the four horsemen of the Apocalypse, it is unquestionably one of the major pestilences of war; there is no more sensitive barometer of national privation and suffering. In World War I, the tuberculosis mortality in all combatant countries rose within the first year and climbed steadily until after the armistice. In France, England and Germany, the rates practically doubled, and even in this country the mortality in 1918 was 50 per cent higher than that in the preceding few years. In the United States, the total deaths from tuberculosis at least equaled the losses in battle in any year of the war.

Incomplete reports from Europe show that tuberculosis had again definitely increased in 1940, and preliminary data here indicate that nearly half the states experienced a slight rise in mortality in 1941. With the prospect of a war longer, more inclusive and far more exhausting than the last, it is high time that we define the problems of tuberculosis under wartime conditions and organize all available control measures in the civilian population as well as in the armed forces.

Essentially, the problems of control are the same in war and in peace: early recognition of cases, prompt hospitalization of those needing treatment, examination of family contacts, maintenance of adequate nutrition, good housing and a reasonable sense of security. The great problem is how to attain a semblance of such conditions with restricted food supplies in a situation that calls for the expenditure of the utmost effort of which we are capable.

The first line of defense is the maintenance, at all costs, of the very effective control organization that has been built up in the last forty years. Although our sanatoriums and clinics have not been the only factors responsible for the decline of 80 per cent in the tuberculosis mortality in that period, they are the most effective weapons we possess for checking any upsurge of the insidious enemy. Prevention, far more than treatment, has been responsible for the gains that have been made, and so long as we prevent the spread of infection from open cases we shall be able to check the infiltration of our population that results in ultimate disaster.

At the beginning of the present war, the English promptly discharged to their homes a large number of patients in tuberculosis sanatoriums to make room for expected military casualties. When it was found that the beds were not needed, these tuberculosis cases were gradually returned to their hospitals, but the tuberculosis service was seriously disrupted and the damage that resulted from returning a large number of patients with contagious lesions to their homes and communities is hard to estimate. It is to be hoped that we profit by our neighbor's experience and retain, so far as possible, the exceptionally adequate sanatorium system we have built up.

Recruitment of physicians and nurses for military needs is bound to throw additional burdens on local boards of health, which have the primary legal responsibility for tuberculosis control. It is essential that reporting of cases be prompt and complete and where every doctor's load has been doubled he must depend more and more on the local public-health nurse for the follow-up and instruction of tuberculosis patients and their families that are so vital a part of prevention. When the patient has gone

\*A "Green Lights to Health" broadcast given through Station WAAB by Dr. Alton S. Pope on Saturday, February 7, and sponsored by the Public Education Committee of the Massachusetts Medical Society and the Massachusetts Department of Public Health.

failed to respond to specific antiserum, that sulfapyridine had a more marked effect on the pneumococcus but also resulted in more toxic reactions, which often caused earlier cessation of therapy than was considered optimal. That sodium sulfapyridine allowed preenteral administration of this drug during the critical vomiting period, that sulfathiazole caused only half as much nausea and vomiting but that larger doses were necessary on the whole to maintain similar blood levels, because of the more rapid metabolism of this drug, and that sulfadiazine results in nausea and vomiting in only 10 per cent of patients, and is generally a less toxic and more effective drug, but is still not ideal. Sulfadiazine is like sulfathiazole—in its direct contrast to sulfanilamide—in its negligible effect on erythrocytes. Agranulocytosis is not unknown in these two more recent compounds, especially after long periods of therapy, and toxic rashes also occur in 4 to 5 per cent of cases under the same circumstances.

The most serious complications are those involving the urinary tract. Fortunately, however, large amounts of fluids can be administered with sulfathiazole and sulfadiazine, without excretion of the drugs in proportionately large amounts—as with sulfanilamide. Also, these compounds have the advantage of being more soluble in the acetylated form. Sulfapyridine usually causes pain and hematuria as initial manifestations, and the crystals are deposited along the level of the tubules, thereby allowing early diagnosis and halting. Sulfathiazole therapy, on the other hand, may result in anuria without any previous manifestation because its crystals may be deposited in the tubules themselves. Sulfadiazine may also cause anuria, but only rarely if the urinary output is kept above 1500 cc per twenty-four hours.

In a recent series at the Boston City Hospital, the gross mortality with sulfadiazine was only 10.7 per cent. For patients under fifty years of age it was 2.9 per cent and in the nonbacteremic cases 7.6 per cent. This contrasts with 21.6 per cent for patients over fifty years, and 24.7 per cent for those with bacteremia. Nineteen per cent of the patients had bacteremia. The mortality in the armed forces during the present war, therefore, should not exceed 2 per cent, in contrast to that of 25 per cent in World War I, it was estimated.

As a result of experiments on the relative efficacy of the four common sulfonamide compounds on the pneumococcus, hemolytic streptococcus, *Staphylococcus aureus* and the Friedländer bacillus,—as well as on their toxicities—it was concluded that sulfadiazine is thus far the drug of choice in all pulmonary infections.

Specific antipneumococcus serum is still useful in cases in which the responsible bacterium becomes resistant to chemotherapy. The only other reason for substituting serum for drug therapy is the onset of serious toxic symptoms although serum may be a useful adjuvant when there is a second positive blood culture or a very severe bacteremia. Second blood cultures should always be taken when the fever lasts more than twenty-four to thirty-six hours on chemotherapy. Chemotherapy with the sulfonamides may be started with a low leukocyte count so long as it is not due to previous administration of the drug and there are a reasonable number of granulocytes. The onset of drug fever, rash and delirium on the seventh to the tenth day is obviously not caused by pneumonia and the pulse usually remains slow.

When a patient suffering from chronic asthma develops fever, it is often well to administer some sulfonamide for sputum examinations in such cases invariably reveal the presence of pathogenic bacteria. Such therapy should be in addition to the usual asthma treatment for without the supplemental action of the latter, these patients do poor-

ly. The same line of attack in those with fever and congestive heart failure often leads to the success of otherwise inefficient cardiac therapy. Chemotherapy with the sulfonamides in such cases, however, should not be continued if there is no improvement in twenty-four to forty-eight hours. If the temperature shows an immediate response, treatment should be carried on for about five days.

Dr Finland discussed influenza and its complications. During the epidemic a year ago, a virus identified as influenza A was isolated in many cases, and a measurable antibody titer found. There were an unusual number of staphylococcal pneumonias of marked severity. These patients were usually sick about two or three weeks, and although there was a tendency for the formation of lung abscesses and empyema, recovery was the rule. On the other hand, there were patients who had a sudden recurrence of signs and symptoms shortly after their apparent recovery from the grippe, with severe cyanosis, cough, inability to rise sputum and sudden death. The pathological findings in these patients were similar to those of influenza patients of World War I. It is impossible to determine how many of these changes are attributable to the virus infection and how many to the superimposed pneumonia, therefore the etiologic agent of the latter should be treated, since there is as yet no adequate therapy for the virus of influenza. The question is often raised whether all influenza patients should be treated with sulfonamides but Dr Finland is not in favor of such a procedure except in epidemics in which there are many pulmonary complications and persistent fevers, and bacteria are cultured.

In conclusion Dr Finland answered questions. Fastness to the sulfonamide drugs is probably not a common or significant occurrence. All susceptibility to these drugs is relative, and if fastness is developed in any case, there is no use in attempting to substitute one drug for another, for these cases develop fastness to all.

No truly characteristic temperature chart is caused by drug fever, but there is usually not a commensurate increase of pulse and the patient does not look so ill as the chart indicates. Such a fever seldom occurs in less than a week, except rarely with sulfathiazole or when the patient fails to report previous treatment by his own physician.

Vaccines do not seem to offer much hope. There is no sound basis for their use as a protection against pneumonia, for there are about sixty strains of the pneumococcus and forty of the streptococcus, besides an unknown number of staphylococcal strains. This mitigates against the inclusion of all strains and anything less could not be considered adequate protection against any given case of pneumonia. Furthermore, staphylococcal and streptococcal vaccines afford only a temporary immunity, and the pneumococcus cultured from the throat is usually not the responsible organism in lobar pneumonia and therefore cannot be used as a criterion of what to include in a vaccine. The use of vaccines against influenza, however, may be important in the future. At present vaccines containing influenza A and the virus of dog distemper protect the ferret but are only suggestively valuable in man. Their efficacy appears to vary from place to place but may be increased in the future.

Serum therapy of pneumonia has not been entirely supplanted but is used in specific cases, namely, in patients over fifty years of age in those who suffer from chronic alcoholism, particularly delirium tremens and in those who fail to respond to chemotherapy. Dr Finland issued a caution against a false sense of security on the basis of a falling temperature in patients treated with sulfapyridine for this drug has an antipyretic as well as bacteriostatic

effect. The response to sulfathiazole and sulfadiazine is slower, so far as the temperature chart is concerned, but the patient invariably feels and looks better even before there is any temperature response. In children, all drugs are apparently efficacious and are less toxic. In fact, the mortality from pneumococcal pneumonia in infants and children has decreased from 30 to 3 per cent since the advent of chemotherapy, and serum is seldom necessary.

## BOOK REVIEWS

*Trauma and Disease.* Edited by Leopold Brahdly, M.D., and Samuel Kahn, M.D. Second edition. 8°, cloth, 655 pp., with 13 illustrations and 13 tables. Philadelphia: Lea and Febiger, 1941. \$7.50.

This book is a symposium on the relation of trauma to diseases of the various organs. The many authors are well qualified to write on their subjects. Such names as Paul White, Hugh Cabot, George Blumer and Elliott Joslin give a note of authority that a single author could not begin to achieve.

A great many unjust settlements for injuries are made largely because some authority such as this book has not been consulted by those who make the final decisions. Past decisions are unreliable in establishing liability or fair compensation. The new knowledge of disease, based on the study of pathology and physiology, calls for a new legal interpretation of disease as related to trauma. In this development, the present work will be a valuable aid.

Each organ or system of the body is considered separately, and the material is arranged so that reference is readily made to any desired subject. The book should be of great value to those members of the medical and legal professions who deal with compensation cases.

*Cardiac Classics: A collection of classic works on the heart and circulation, with comprehensive biographic accounts of the authors.* Compiled by Frederick A. Willius, M.D., and Thomas E. Keys, M.A. 4°, cloth, 858 pp., with 102 illustrations. St. Louis: The C. V. Mosby Company, 1941. \$10.00.

The authors have performed a useful service for the medical profession, especially for those interested in the development of the knowledge of cardiovascular disease, by assembling in one volume some of the more important original contributions. This book begins with a brief account of the influence of certain cardiac classics on the development of modern cardiology. The introduction is followed immediately by a complete transcription of William Harvey's classic treatise on the circulation of the blood, as translated by Robert Willis, of Barnes, Surrey, England, in 1847. The extensive quotation from Harvey is followed by contributions in whole or in part from fifty other authorities, ending with Sir James Mackenzie, Sir William Osler, James B. Herrick and Oliver Wendell Holmes ("The Stethoscope Song—A Professional Ballad").

No two persons would agree in every detail concerning the value of many of these contributions. The reviewer would like to have seen something quoted from several of the more important earlier writers not included here, such as Lower, Bonetus, Vieussens and Lancisi, but he has been compensated by an opportunity to become acquainted with several authors whose works he had not previously read.

One of the helpful and interesting parts of the book is the collection of brief biographies preceding each quotation. Among the other authors quoted whose names and works are best known are Malpighi, Hales, Senac, Morgagni, Auenbrugger, Heberden, Withering, Corvisart,

Laennec, Hope, Stokes, Flint, Roger, Steell, Broadbent, Einthoven and Keith.

At the end of the book are short tables giving the correlation of these classics with other contemporary historical events and a list of biographical references. A good many interesting illustrations are included, such as the pictures of some of the authors themselves, occasional title pages, pulse tracings, Laennec's stethoscope, and drawings of normal and pathologic hearts.

*Communicable Disease Control: A volume for the health officer and public health nurse.* By Gaylord W. Anderson, M.D., and Margaret G. Arnstein, R.N., M.A., M.P.H. 8°, cloth, 434 pp., with 13 tables. New York: The Macmillan Company, 1941. \$4.25.

This volume, which furnishes concise information in a clear form on the subject of communicable-disease control for the community, is a very valuable addition to the literature.

The chapter on the infectious process, in which an analogy is drawn between the effect of forces acting on a block in the physics laboratory and the forces of infection and resistance, is clearly expressed without recourse to unfamiliar terms, and gives one of the clearest presentations available in the literature.

General control measures are discussed, embodying the principles without undue verbiage. Legal basis for control is cited, and the various administrative agencies for control are briefly reviewed. There is an excellent chapter on the role of the public-health nurse, and one on the home care of patients with communicable diseases.

The book is consistent in discussing individual diseases. The pattern is always obvious, and one can immediately find the desired information under its appropriate heading for each disease discussed. The order is: occurrence of disease, the etiologic agent, the reservoir of infection, escape from the reservoir, transmission, entry and incubation period, susceptibility, control methods and minimizing ill effects.

The volume, which should be in the hands of every public-health official and nurse, will be a useful addition to the library of every general practitioner.

*Rheumatic Fever in New Haven.* Edited by John R. Paul, M.D. 8°, paper, 176 pp., with 22 tables and 45 charts. Lancaster, Penn.: The Science Press Printing Company, 1941. \$1.00.

This is an epidemiologic study of rheumatic fever. Although the etiology of this disease is obscure and there are no definite tests available for diagnosis, much can be learned of the public-health aspects of rheumatic fever by the statistical method. The incidence of the disease was calculated from hospital admissions in the three large hospitals in New Haven. The active cases made up 1.2 per cent of the admissions to the medical services. The incidence of rheumatic heart disease was found to be somewhat lower among a group of relatively well-to-do students of Yale University, but the factor of poverty does not seem to have so important a predisposing role in determining the incidence of rheumatic heart disease as it does in tuberculosis. The disease is distributed fairly evenly among people of different nationalities. The clinical entity of rheumatic fever is rarely precipitated in a normal person as a result of his first contact with the infectious agent. The author believes that the infant must grow up to be a rheumatic. Poverty and crowding, according to this study, do not appreciably enhance the prevalence of rheumatic fever.

(Notices on page ix)

# The New England Journal of Medicine

Copyright, 1942, by the Massachusetts Medical Society

VOLUME 226

APRIL 23, 1942

NUMBER 17

## VOLKMANN'S ISCHEMIC CONTRACTURE\*

### An Analysis of Its Proximate Mechanism

PHILIP S. FOISIE, M.D.†

BOSTON

SINCE 1871, when von Volkmann first described the contracture deformity that bears his name, has commonly been accepted as a complication of the improperly treated supracondylar fracture of the humerus. This paper presents evidence that Volkmann's ischemic contracture has no essential connection with such a fracture or any other specific injury but is the result of ischemic necrosis produced by segmentary arterial spasm of the main artery to an extremity, with reflex spasm of the collateral circulation. Thus, a subtotal ischemia is produced, and the muscle bellies, which have the greatest demand for arterial blood and are therefore the most vulnerable tissue to loss, are the first affected. Gangrene of the fingertips or partial or even complete gangrene of the extremity would result if this spasm continued to a sufficiently severe degree, but where Volkmann's contracture is to be the only result, some improvement in the arterial supply intervenes. This vasomotor activity is under control of the sympathetic nervous system, and will be discussed more fully after the actual clinical picture has been considered.

The problem can be further defined by the statement that only the acute stage of Volkmann's contracture is concerned in this study. Whatever may be the responsible factors, the condition initially is one of impaired circulation. In the old cases of established deformity, normal blood supply has returned, and the problem is entirely one of correcting existing deformity by physiotherapy, tendon lengthening, bone shortening and so forth. These procedures have been discussed elsewhere, and are not considered in this paper, which is limited to a discussion of

Volkmann's contracture in its acute stage, the actual mechanism producing the ischemia and the logical methods of correcting the causative lesion; the goal of treatment is to restore adequate circulation before irreparable damage is done, and thus to avert contracture deformities.

### RECENT CLINICAL EXPERIENCE

In the literature of the last five years, most particularly in the last two years, from France, England, Switzerland and occasionally from South America, numerous articles, mostly from unrelated sources, have described the operative findings in explored cases of early Volkmann's syndrome. Thirty of these case histories were reviewed, and findings of the various operators were strikingly similar. The antecedent injury was usually a fracture or bullet wound of the upper arm. In about twenty-four hours, definite signs of ischemia appeared: the hand became cold and swollen, with usually a pale cyanosis, and the fingers became functionless. Pain was a prominent symptom, especially on any attempt at motion of the fingers, either active or passive. The radial pulse was absent. If the condition was further observed, the next day the fingers usually assumed a position of flexion, and any attempt to straighten them caused considerable pain. When apparatus was used to maintain extension of the fingers, the patient could not tolerate it for long, even with repeated doses of morphine, and it invariably had to be removed. In these cases, the surgeon, after intervals varying from twenty-four hours to three weeks, finally decided to explore the injured site. It is interesting that in most cases the surgeon had not explored such an injury before and was not prepared for what he found. He went in expecting to find some mechanical obstruction to the arterial flow, angulation of the artery over the

\*From the Fourth Surgical Service, Boston City Hospital.

†Assistant in surgery, Tufts College Medical School; assistant to visiting surgeon, Boston City Hospital.

proximal fragment or pressure of fragments on the artery, hematoma or some other mechanical disturbance that he hoped to be able to correct; accordingly, these men could certainly not be accused of the possible inclination of an enthusiast to read into his findings something that he was looking for. This, I think, gives added weight to the observation that in every case a profound segmentary arterial spasm was encountered. The operative note might have been as follows:

A longitudinal incision was made medial to the biceps tendon, and in the lower half of the incision, no bleeding occurred. The muscle, which herniated through the superficial fascia when it was incised, appeared gray and lifeless. There was some extravasated old blood, but no hematoma under pressure. The median nerve was not remarkable. The brachial artery, however, presented a most astounding picture. At a point about 2 cm. above its bifurcation, it was pulsating normally, was even perhaps a little dilated, but there it suddenly became narrowed to a stringlike size extending down into the radial and ulnar branches.

The foregoing description is not taken from any one case but is a synthesis of so many reports that it is almost universally applicable. The methods by which these surgeons attempted to treat the patients are discussed below. The important point is that in patients presenting definite signs of an early Volkmann's syndrome with an absent radial pulse, a cold pallid ischemia and a beginning flexion deformity of the fingers, exploration generally revealed a segmentary spasm of the main artery. Although arterial spasm of varying degrees has been recognized in many peripheral vascular disorders, it has not until very recently been suspected of being responsible for such severe ischemia, and this series of cases establishes arterial spasm as a phenomenon to be reckoned with.

#### PATHOLOGY

As a background for this discussion of how the established Volkmann's contracture is produced by this mechanism, a review of its pathology is necessary. It is essentially an atrophy of the flexor muscle bellies, whose destruction results in an apparent shortening of the flexor tendons, pulling the fingers and sometimes the wrist into acute flexion (Fig. 1). In the less severe cases, by flexion of the wrist, the fingers can be extended and vice versa, but extension of both fingers and wrist is not possible at the same time. In the severer cases, neither can be done.

One of Griffiths's<sup>1</sup> contributions to this subject is his very precise description of the morbid anatomy. The gross picture, which is one of central degeneration of the muscle bundle, is duplicated histologically by only one other condition, infarction. In both, there is a picture of mass

necrosis; the most extensive degeneration occurs in the center of the muscle sequestrum, and cellular activity and fibrosis take place only at the periphery, which is surrounded by a sheath of

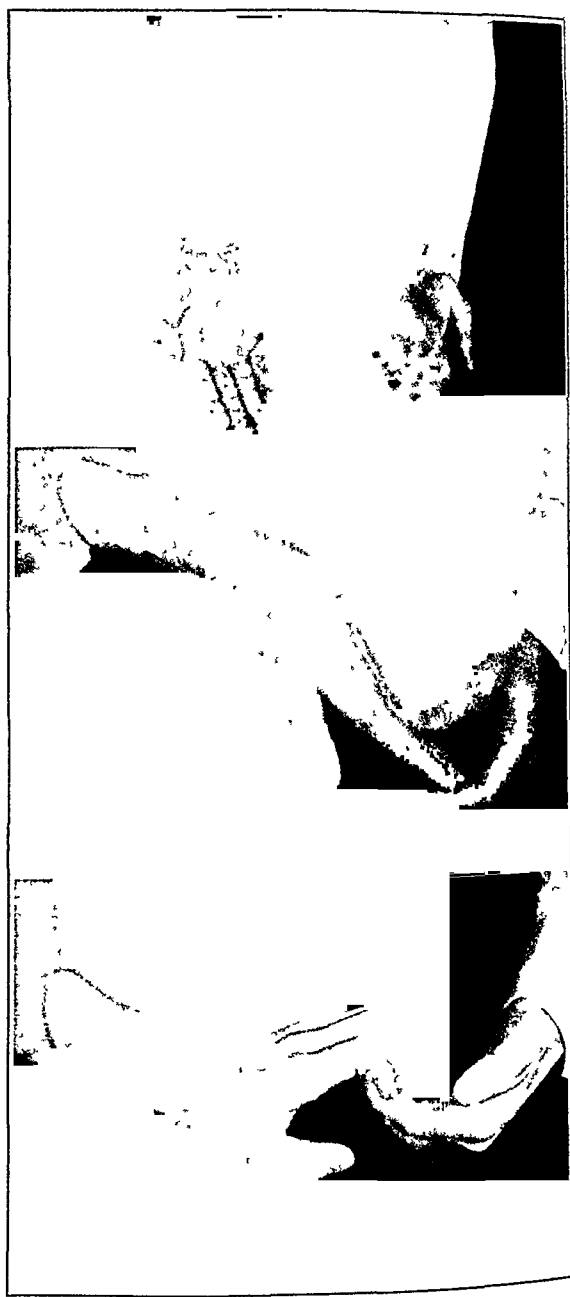


FIGURE 1. *Clinical Deformity in a Case That Was Not Severe to Begin with and That Was Further Improved by Operative Lengthening of the Flexor Tendons.*

*Note the atrophy of the forearm. With the wrist flexed, the fingers could be fully extended, and with the fingers flexed, the wrist could be fully extended, but both could not be done at once.*

dense fibrous tissue. In the center of the mass, the muscle fibers lose their nuclei and cross striations, and fuse into a homogeneous mass, little more than a defining membrane separating them (Fig. 2). As the periphery is approached, some

signs of function are preserved, and there is an area of intense cellular activity, both fibroblastic and phagocytic (Fig. 3). This picture is in contrast to muscle degeneration from all other causes, such as denervation and sepsis, when the appearance is one of diffuse interfibrillar fibrosis (Fig. 4). This histology should be kept in mind when one considers the mechanism of the

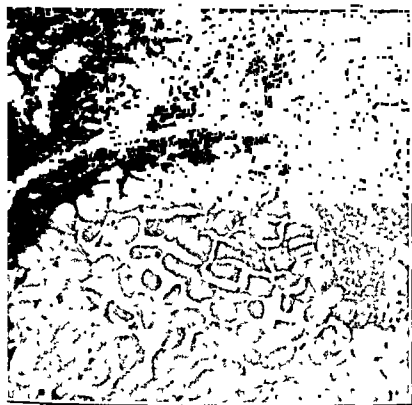


FIGURE 2. Low Power View of a Cross Section of the Flexor Muscles of the Forearm in a Case of Volkmann's Contracture.

*Note the mass necrosis of the muscle bundles, with the greatest destruction in the center and with the cellular activity limited to the periphery (Griffiths<sup>1</sup> reproduced with permission of the publisher)*

ischemia. It is also of value in animal experimental work in determining whether or not a true Volkmann's contracture has been produced

#### ETIOLOGY

The fact that supracondylar fracture of the humerus is the commonest initial injury that Volkmann's contracture may complicate has perhaps led many to associate the contracture exclusively with such fractures. The location of this fracture and the related displacement that commonly occurs unquestionably bring into play many factors tending to impair circulation of the forearm. Among these are the possible angulation of the brachial artery over the edge of the proximal fragment, the damage to soft tissue from spicules of bone and, most commonly mentioned, the possibility of hemorrhage into the antecubital fossa, with the formation of a hematoma confined by the unyielding deep fascia and thereby tamponading the venous return. It has been pointed out that such a pressure hematoma is especially effective at this point because the venous

return from the forearm converges into a plexus that is particularly vulnerable to local pressure. If to this is added a difficult and unskillful reduction, and the application of some constricting apparatus in a position of acute flexion, the *coup de grâce* may be administered to the circulation of the forearm.

That this is a reasonable and adequate picture of circulatory embarrassment cannot be denied and, in fact, very logically explains its almost unchallenged acceptance for so long. And I have no desire to suggest that these factors are not important. It is obvious that in any situation in which ischemia is present, any factor that impairs circulation in any way must never be tolerated. No doubt, it is possible to shut off the circulation to any extremity by overly tight splints, and perhaps on occasions this has been done. It is self-evident that prompt, gentle and skillful reduction, and properly applied fixation are fundamental



FIGURE 3. High Power View of the Specimen in Figure 2.

*Note that the muscle fibers near the periphery retain their cross striations and are more nearly normal (Griffiths<sup>1</sup> reproduced with permission of the publisher)*

essentials. Given these, this syndrome has developed right under the eyes of the most capable surgeons; even when they had the opportunity of treating the patient from the beginning.

The chief evidence that the factors of venous occlusion and constriction of overly tight apparatus do not constitute the essential mechanism of Volkmann's ischemia is that actually the syndrome commonly develops in the complete absence of such causes. In cases of supracondylar fracture in which these factors might reasonably be expected and in which the fracture site has been

exposed by open operation, the subfascial hematoma as such has rarely been found. There is a certain amount of old blood clot and loose hemorrhage in the tissues as at any fracture site, but no specifically confined mass. The most approved treatment has consisted in multiple drainage incisions through the fascia; but this procedure, in addition to the removal of all apparatus, has in many cases not improved the circulation, and when improvement occurs, the artery itself has usually been exposed and freed. I consequently believe

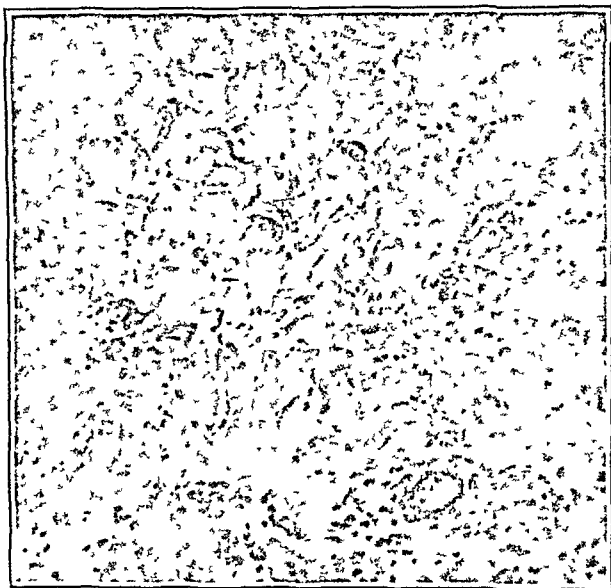


FIGURE 4. Cross Section Showing the Histologic Picture of the Muscle Atrophy from All Other Causes.

*Note the diffuse interfibrillar fibrosis, as contrasted with the picture in Figures 2 and 3. This difference seems to be the best argument against the theory of venous occlusion, since one would expect the above picture if Volkmann's contracture was the result of venous occlusion, with edema and retention of metabolic waste products (Griffiths<sup>1</sup>: reproduced with permission of the publisher).*

that the procedure has fortuitously achieved the result of releasing reflex arterial spasm.

Further evidence against these factors is that this particular injury, which most favors their presence, is by no means the only one that Volkmann's ischemia may follow. It occurs in practically all fractures of the upper extremity, even those as far removed as the clavicle, in several other injuries to soft parts in which no fracture has occurred, and in similar injuries of the lower extremities. Hill and Brooks,<sup>2</sup> in 1936, reviewed the literature and found 123 cases without the previous application of any constricting bandage or splint, and 28 cases in which there was neither any fracture nor constricting bandage or splint. Furthermore, many cases of soft-tissue injury with only moderately severe trauma are described, and

Griffiths<sup>1</sup> reports 3 cases following arterial embolism from heart disease in which there was no trauma of any kind.

These facts may afford some comfort to the surgeon who has seen this complication develop in a patient under his care. They suggest that the proximate mechanism is initiated by the injury itself rather than by the treatment, and that it is an ischemia intrinsically arterial in which other factors are only secondary.

#### ARTERIAL SPASM

Leriche<sup>3</sup> has written a great deal on circulatory equilibrium, which is ensured for each structure by the action of the vasomotor nerves. These nerves adapt the local circulation to the regional requirements by vasoconstriction or vasodilatation as a result of constantly changing stimuli. Leriche differs from many physiologists in his opinion that the sympathetic system contains sensory as well as motor fibers and that the sympathetic ganglion plays the role of reflex center. It is easy to believe, therefore, that the sympathetic system may have a definite role to play in injury by which a local temporary arterial spasm may be set up to prevent overextravasation of blood or fatal hemorrhage from a severed artery. If these stimuli are not removed, or if the patient has an especially labile vasomotor reflex, the spasm may persist beyond its physiologic requirements and may even spread to include the collateral circulation.

Varying degrees of arterial spasm are encountered in many peripheral vascular disturbances. Homans's<sup>4</sup> book on circulatory diseases of the extremities contains a whole chapter on this subject. There is, no doubt, a difference in the mechanism of production between a generalized vasoconstriction and local segmentary spasm; the former is probably due to central innervation and the latter is possibly the result of a local reflex. This point was brought out by Homans<sup>5</sup> in discussing a case of his in which an adequate and satisfactory ganglion injection failed to relieve a local arterial spasm; about twenty-four hours later, the foot became suddenly flushed with an extensive vasodilatation. He logically concluded that local spasm may be effected by a distal reflex arc that does not include the ganglion. Injury need not directly affect the vessel to produce arterial spasm. The following case illustrates this fact.

CASE 1. A young, muscular, colored man was admitted to the Boston City Hospital immediately after an altercation with some "friends." The admission diagnosis was bullet wounds of the chest and of the right upper arm and surgical shock. I happened to be in the hospital at the time, and I went to see the man immediately, being concerned particularly about the shock aspect of the diagnosis. To my surprise, I found him reclining on one elbow,

chewing gum, and grinning with considerable self satisfaction. Obviously, he was not in any surgical shock. I picked up his wrist to feel his pulse, but there was none. The house officer who had admitted him had apparently made the same finding, which accounted for the shock diagnosis, but had neglected to feel the opposite arm, where the patient had a perfectly good full pulse and a systolic blood pressure of 140. Examination of the chest revealed that the bullet wound was superficial, and there were no signs of damage to the lungs, the problem boiled down immediately to the wound of the right upper arm, where there were bullet wounds of entrance and exit through the fleshy portion of the biceps. There was some swelling of this area, but the arm was not grossly distended or tense, and x-ray examination revealed no fracture of the humerus. We believed that some damage had probably been done to the brachial artery, and immediately explored it. Going through the muscle, we found a certain amount of extravasation of blood but no gross hematoma, at least, no hematoma under pressure sufficient to occlude the artery. On exposing the artery itself, we were surprised to find that at a point about 2 cm above its bifurcation, it was constricted to a stringlike structure. We picked it up and freed it, and followed it along down with the idea of seeing how far this constriction continued, when all of a sudden it began to pulsate and filled with blood. A bystander who was asked to palpate the radial pulse reported that there was good pulse at the wrist. We simply closed the wound, and the patient made an uneventful recovery and never subsequently had any circulatory disturbance in this extremity.

This patient had no direct trauma to the artery, nor was there sufficient extrinsic pressure to occlude it mechanically. He did not, at least at the time of operation, have the essential elements of a Volkmann's contracture because there was still good collateral circulation. Left alone, he might either have spontaneously relieved the local spasm or later developed reflex collateral spasm. I should probably treat a similar case by ganglion injection, followed by surgical intervention only if collateral circulation became impaired.

Sometimes, segmentary spasm is produced by minor injury to the arterial wall that is not sufficient to occlude the artery by the damage per se but causes the artery to occlude itself. Griffiths<sup>1</sup> describes a patient who was pulseless after satisfactory reduction of a supracondylar fracture. He explored and found no subfascial hematoma, but did find a hematoma no larger than a millet seed in the anterior wall of the brachial artery near the site of fracture. Despite the small size of this hematoma, the brachial artery and its radial and ulnar branches were collapsed and pulseless. Mobilizing and stripping the brachial artery produced no change, but after resection of the damaged portion, the circulation made a complete recovery and no deformity resulted. Griffiths also mentions a case in which the brachial artery showed a very localized intramural rupture, which presented complete spasm from the subclavian artery downward. Several cases are presented in the

literature in which resected sections of artery showed, on pathological study, small defects not grossly visible.

Montgomery and Ireland<sup>6</sup> encountered localized arterial spasm in 2 cases, and were stimulated to search the literature for others; in 1935, they reported 44 cases of what they termed "traumatic segmentary arterial spasm," resulting from all kinds of trauma, but of which 26 were the result of gunshot or high explosive injuries. In 1940, Gage and Ochsner<sup>7</sup> published an excellent report in which arterial spasm is discussed quite fully. They were dealing with the subject of operative procedures on peripheral arteries. They mentioned particularly a so-called "butcher's injury," which results from slipping of the knife during the skinning of beef; a stab wound of the upper medial aspect of the thigh commonly results with injury of the femoral vessels or perivascular tissue in the upper end of Hunter's canal. They noted that in many cases, even when the vessels were not severed, reflex vasospasm was of such severity that the clinical manifestations were identical with those of complete arterial occlusion.

Arterial spasm is also seen following lodgment of emboli, and in fact may result from any disturbance of the peripheral circulation. Homans<sup>4</sup> states that it is known to occur with venous thrombosis, especially the inflammatory sort. One writer<sup>8</sup> graphically referred to this spasm as "arterial colic."

#### COLLATERAL CIRCULATION

Griffiths's<sup>1</sup> Hunterian Lecture on Volkmann's contracture is the most modern complete discussion of this subject in the literature, and deserves the careful study of everyone interested in the subject. Of the many contributions he makes, I think that the most important is his demonstration by animal experiments that the key factor in the development of Volkmann's contracture is the loss of the collateral circulation. The danger to the peripheral tissues of a main artery in spasm is not so much the loss of the artery itself as a blood-carrying channel as it is the possibility that this spasm may spread to include the collateral circulation as well. Normally, with the main vessels intact, the collateral circulation functions only to a small percentage of its full potential, but its presence affords an alternate route that can, if necessary, be developed to furnish adequate circulation in lieu of the main artery. There are certain anatomic weak points in this system; namely, the common femoral artery, the carotid artery at its bifurcation and the popliteal arteries, about which collateral circulation is not abundant; the regions about the shoulder, elbow, hip, hand



and foot, however, are abundantly supplied. When occlusion of the main artery is a gradual process, simultaneous hypertrophy of the collaterals occurs, and no embarrassment of circulation results. The strain is much greater on the collaterals when the occlusion of the main artery is sudden, and circulation is further imperiled by the fact that the collaterals are subject to the same sympathetic control as the main vessel. Thus, a vicious circle is possible in that if spasm of the main artery becomes fixed beyond its normal physiologic intentions, the same condition may spread to the collaterals at a time when their increased function is needed. It has been shown by oscillometer readings that, with a main artery occluded, reflex vasospasm not only may obstruct the collateral circulation of that extremity but also may affect the opposite side, and even extend to the lower extremity. Thus, without extrinsic pressure, a total or subtotal ischemia may be produced that will result only in muscle atrophy if the ischemia is relatively temporary, and in varying degrees of gangrene if the ischemia is prolonged.

Leriche et al.,<sup>9</sup> working with dogs, were able to resect all the large arteries of the hind legs, beginning distally and operating in eight or nine successive stages spaced at intervals of from ten to thirty days. In this manner, they removed the posterior tibial, the anterior tibial, the femoral, the inferior gluteal, the lateral sacral, the hypogastric, the external iliac and, in the final stage, the common iliac arteries and the bifurcation of the aorta. Carrying out this procedure, they encountered only occasional temporary edema, which rapidly disappeared. These dogs, literally "without arteries," were able to run, stand on hind legs, and jump as normal animals. When the authors attempted initially to resect the common iliac arteries and the bifurcation of the aorta, all the animals promptly died, but if this procedure was preceded by resection of the lumbar sympathetic ganglions, the animals were only slightly disturbed by this extensive arterectomy.

Gage and Ochsner<sup>7</sup> discovered the value of developing the collateral circulation by ganglion block prior to operative procedures on peripheral arteries.

It is evident that good collateral circulation is capable of amply supplying all the needs of the peripheral tissues, and that the chief danger in cases of main-artery occlusion lies in the degree of constriction or dilatation of the collaterals that are under sympathetic vasomotor control. Griffiths, in his animal experiments, showed this loss of the collateral circulation to be the determining factor in the development of Volkmann's contracture.

## TREATMENT

It should be emphasized that time is a major factor in treatment. This syndrome is a progressive one in which more and more damage is done. The value of early action is apparent. In the first place, all measures favoring circulation generally are of fundamental value. These include elevation of the part, removal of any apparatus or circular bandaging, and the application of mild external warmth.

The next logical step is the interruption of the sympathetic reflex arc. Theoretically, one might expect to accomplish this by ganglion injection, periarterial sympathectomy or arterectomy. Ganglion block, which is the simplest of these methods, should be tried first. Its results will be apparent at once, and if the procedure is successful, an open operation is avoided. The following case illustrates its use.

CASE 2. A 53-year-old woman was admitted to the Boston City Hospital on September 1, 1941, with a trimalleolar fracture of the left ankle. A Kirschner wire was inserted for traction, and open reduction was later performed under an Esmarch bandage. The operation lasted an hour and a half. The next day, the foot was cold, cyanotic, swollen and painful. The dorsalis pedis and popliteal arteries were not palpable. A lumbar block was done that afternoon. Forty cubic centimeters of novocain was injected, about 15 cc. through each of three needles, and 15 minutes after this procedure, the circulation improved. The following day, both the dorsalis pedis and the popliteal arteries were palpable; 1 week later, swelling of the toes was entirely gone, the foot was warm and pink, the wounds were clean, and the chart was flat. The patient had no subsequent circulatory difficulty.

Lumbar block is now a common procedure when peripheral dilatation is desired, and needs no further comment. Injection of the stellate ganglion is perhaps not so familiar, but reports of surgeons in the French army indicate that it is now being frequently employed in the relief of peripheral spasm of the upper extremity. Luzuy,<sup>10</sup> who apparently was called on to attend a large number of fresh injuries, states that he has had occasion to employ this procedure as often as several times a day. The appearance of the Bernard-Horner syndrome within a few minutes is evidence of successful cervical sympathetic paralysis.

The possibility that local arterial spasm may be the result of a local reflex that does not include the paravertebral ganglions means that this procedure cannot be expected to be universally successful; if circulatory improvement is not promptly apparent, or if initial improvement is not maintained, the artery should be exposed. The adherents to the theory of venous occlusion have logically treated this syndrome by multiple inci-

sions through the deep fascia to afford drainage and relieve pressure. This procedure has been successful in cases in which venous congestion was the main secondary factor, producing the arterial spasm that was the proximate cause of the ischemia. It has failed in many cases when other factors were in effect. I believe that it is therefore more logical to approach the problem directly—to expose the artery by careful dissection. This at once accomplishes effective relief of

of circulation resulted in every case, and complete return of normal circulation and function in most cases. In only 1 case<sup>12</sup> did a poor result occur, this patient was said to have had paralysis of the radial, median and ulnar nerves as well, so that the case could hardly be included in a series of pure Volkmann's contractures.

Arterectomy may appear to be a radical procedure,\* and a natural reaction is to try to save the artery and hope to reestablish function of



FIGURE 5 Arteriographic Study in a Case of Volkmann's Contracture  
Note the segmentary spasm of the lower end of the brachial and the upper ends of the radial and ulnar arteries (Leisner<sup>12</sup>)

any abnormal venous pressure, determines whether any local trauma to the artery has been sustained, and affords opportunity for complete sympathetic interruption by periarterial sympathectomy or arterectomy.

Concerning the respective values of these two procedures, there is some difference of opinion among those surgeons who have had some experience in their use. In the series of 30 cases mentioned above, arterectomy was performed in 10, periarterial sympathectomy in 5, and various procedures in the rest—including freeing up of the artery, novocain injection, ligation and simple loose closure. The arterectomy group invariably gave the best results. Definite improvement

this blood carrying channel. Objections to this are that the alternative periarterial sympathectomy on an extremely contracted artery may be technically difficult, and that interruption of the sympathetic control is the main goal in view. Arterectomy has the advantage of complete interruption of the reflex, in addition to the removal of a segment of artery that possibly contains a small break or tear, not grossly visible, but sufficient to maintain continued abnormal sensory stimuli. Arteriographic studies in late cases of Volkmann's contracture have shown a persistently interrupted segment of the main artery (Fig 5), although satisfactory

\*A 3 cm. to 5-cm. segment of the contracted artery is removed with simple ligation of both free ends.

and foot, however, are abundantly supplied. When occlusion of the main artery is a gradual process, simultaneous hypertrophy of the collaterals occurs, and no embarrassment of circulation results. The strain is much greater on the collaterals when the occlusion of the main artery is sudden, and circulation is further imperiled by the fact that the collaterals are subject to the same sympathetic control as the main vessel. Thus, a vicious circle is possible in that if spasm of the main artery becomes fixed beyond its normal physiologic intentions, the same condition may spread to the collaterals at a time when their increased function is needed. It has been shown by oscillometer readings that, with a main artery occluded, reflex vasospasm not only may obstruct the collateral circulation of that extremity but also may affect the opposite side, and even extend to the lower extremity. Thus, without extrinsic pressure, a total or subtotal ischemia may be produced that will result only in muscle atrophy if the ischemia is relatively temporary, and in varying degrees of gangrene if the ischemia is prolonged.

Leriche et al.,<sup>9</sup> working with dogs, were able to resect all the large arteries of the hind legs, beginning distally and operating in eight or nine successive stages spaced at intervals of from ten to thirty days. In this manner, they removed the posterior tibial, the anterior tibial, the femoral, the inferior gluteal, the lateral sacral, the hypogastric, the external iliac and, in the final stage, the common iliac arteries and the bifurcation of the aorta. Carrying out this procedure, they encountered only occasional temporary edema, which rapidly disappeared. These dogs, literally "without arteries," were able to run, stand on hind legs, and jump as normal animals. When the authors attempted initially to resect the common iliac arteries and the bifurcation of the aorta, all the animals promptly died, but if this procedure was preceded by resection of the lumbar sympathetic ganglions, the animals were only slightly disturbed by this extensive arterectomy.

Gage and Ochsner<sup>7</sup> discovered the value of developing the collateral circulation by ganglion block prior to operative procedures on peripheral arteries.

It is evident that good collateral circulation is capable of amply supplying all the needs of the peripheral tissues, and that the chief danger in cases of main-artery occlusion lies in the degree of constriction or dilatation of the collaterals that are under sympathetic vasomotor control. Griffiths, in his animal experiments, showed this loss of the collateral circulation to be the determining factor in the development of Volkmann's contracture.

## TREATMENT

It should be emphasized that time is a major factor in treatment. This syndrome is a progressive one in which more and more damage is done. The value of early action is apparent. In the first place, all measures favoring circulation generally are of fundamental value. These include elevation of the part, removal of any apparatus or circular bandaging, and the application of mild external warmth.

The next logical step is the interruption of the sympathetic reflex arc. Theoretically, one might expect to accomplish this by ganglion injection, periarterial sympathectomy or arterectomy. Ganglion block, which is the simplest of these methods, should be tried first. Its results will be apparent at once, and if the procedure is successful, an open operation is avoided. The following case illustrates its use.

CASE 2. A 53-year-old woman was admitted to the Boston City Hospital on September 1, 1941, with a trimalleolar fracture of the left ankle. A Kirschner wire was inserted for traction, and open reduction was later performed under an Esmarch bandage. The operation lasted an hour and a half. The next day, the foot was cold, cyanotic, swollen and painful. The dorsalis pedis and popliteal arteries were not palpable. A lumbar block was done that afternoon. Forty cubic centimeters of novocain was injected, about 15 cc. through each of three needles, and 15 minutes after this procedure, the circulation improved. The following day, both the dorsalis pedis and the popliteal arteries were palpable; 1 week later, swelling of the toes was entirely gone, the foot was warm and pink, the wounds were clean, and the chart was flat. The patient had no subsequent circulatory difficulty.

Lumbar block is now a common procedure when peripheral dilatation is desired, and needs no further comment. Injection of the stellate ganglion is perhaps not so familiar, but reports of surgeons in the French army indicate that it is now being frequently employed in the relief of peripheral spasm of the upper extremity. Luzuy,<sup>10</sup> who apparently was called on to attend a large number of fresh injuries, states that he has had occasion to employ this procedure as often as several times a day. The appearance of the Bernard-Horner syndrome within a few minutes is evidence of successful cervical sympathetic paralysis.

The possibility that local arterial spasm may be the result of a local reflex that does not include the paravertebral ganglions means that this procedure cannot be expected to be universally successful; if circulatory improvement is not promptly apparent, or if initial improvement is not maintained, the artery should be exposed. The adherents to the theory of venous occlusion have logically treated this syndrome by multiple inci-

sions through the deep fascia to afford drainage and relieve pressure. This procedure has been successful in cases in which venous congestion was the main secondary factor, producing the arterial spasm that was the proximate cause of the ischemia. It has failed in many cases when other factors were in effect. I believe that it is therefore more logical to approach the problem directly—to expose the artery by careful dissection. This at once accomplishes effective relief of

of circulation resulted in every case, and complete return of normal circulation and function in most cases. In only 1 case<sup>11</sup> did a poor result occur; this patient was said to have had paralysis of the radial, median and ulnar nerves as well, so that the case could hardly be included in a series of pure Volkmann's contractures.

Arterectomy may appear to be a radical procedure,\* and a natural reaction is to try to save the artery and hope to re-establish function of

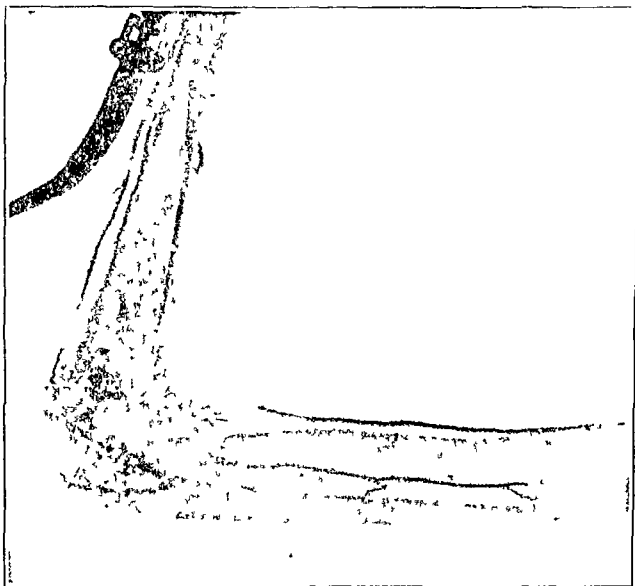


FIGURE 5 Arteriographic Study in a Case of Volkmann's Contracture

Note the segmentary spasm of the lower end of the brachial and the upper ends of the radial and ulnar arteries (Leteru<sup>12</sup>)

any abnormal venous pressure, determines whether any local trauma to the artery has been sustained, and affords opportunity for complete sympathetic interruption by periarterial sympathectomy or arterectomy.

Concerning the respective values of these two procedures, there is some difference of opinion among those surgeons who have had some experience in their use. In the series of 30 cases mentioned above, arterectomy was performed in 10, periarterial sympathectomy in 5, and various procedures in the rest—including freeing up of the artery, novocain injection, ligation and simple loose closure. The arterectomy group invariably gave the best results. Definite improvement

this blood carrying channel. Objections to this are that the alternative periarterial sympathectomy on an extremely contracted artery may be technically difficult, and that interruption of the sympathetic control is the main goal in view. Arterectomy has the advantage of complete interruption of the reflex, in addition to the removal of a segment of artery that possibly contains a small break or tear, not grossly visible, but sufficient to maintain continued abnormal sensory stimuli. Arteriographic studies in late cases of Volkmann's contracture have shown a persistently interrupted segment of the main artery (Fig 5), although satisfactory

\*A 3 cm. to 5 cm. segment of the contracted artery is removed with simple ligation of both free ends.

collateral circulation had eventually been established. If the artery is going to maintain a contracted state, it is of no value as a blood carrying channel, and the removal of this contracted segment is not a circulatory loss.

Leriche et al.<sup>9</sup> urge arterectomy on the ground that a constricted artery that has no blood flowing through it but still has its sympathetic fibers running through its adventitia is in effect not an artery at all, but is an abnormal sympathetic nerve. To my mind, the most surprising feature in the results obtained in this group of cases is the improvement obtained in patients operated on comparatively late. Du Pan<sup>13</sup> reported a case in which arterectomy was performed over three weeks after the onset of symptoms, with complete recovery except for slight hypothermia and interosseus atrophy. This fact throws some doubt on Griffiths's conclusion that irreparable damage is done within the first twenty-four hours; he was probably influenced in this belief by the fact that flexion deformity of the fingers is one of the earliest signs to appear, but at this stage it could hardly be the result of cicatricial contraction. In discussing Massart's paper, Mutuel<sup>14</sup> brings up this point. He cites the observation that with a patient asleep or under an anesthetic, pressure of a blood-pressure cuff causes the fingers to flex. Browne<sup>15</sup> has spoken of this flexion as the position of "physiologic rest," and I believe that its assumption in the early stages simply means that the patient naturally assumes the position that is most comfortable and causes the least traction on the disturbed area. The subsequent permanent flexion deformity is the result in part of the fact that fibrosis occurs with the fingers in flexion to begin with; this deformity is further developed by subsequent cicatrization.

#### DISCUSSION

The mechanism of production and of the possible results of arterial spasm is a field new enough to be filled with opportunities for further study and many interesting possibilities, which are by no means limited to various circulatory disturbances of the extremities; to keep this discussion within reasonable bounds, however, one must for the moment curb any impulse to speculate, and consider only the subject at hand. It has probably always been taken for granted that arterial circulation is adequate unless the main artery is plugged, divided or shut off by external pressure, and therefore the realization that complete ischemia can be developed by the action of the artery walls is rather shocking. Still more interesting is the fact that the major arteries are by no means essential, and that the collateral circulation holds the balance between life and death of the peripheral

tissues. Volkmann's contracture is a result of a relatively temporary subtotal ischemia, which may be initiated by any injury or circulatory disturbance that sets this mechanism into action.

An interesting sidelight is that, because in most cases this complication is probably the result of the initial injury, many surgeons have been unjustly accused of unskillful treatment. Du Pan,<sup>13</sup> after reporting his case, confesses his guilt in this respect. He relates that he had always prided himself on the fact that this complication had never occurred in his clinic, a record that he attributed to painstaking care in reduction and immobilization. He had looked with privately raised eyebrows on the occurrence of Volkmann's contracture in the hands of his confreres, supposing that it would not have happened under his care. His chagrin can be imagined when, in spite of his best efforts, the contracture occurred in his own case. He concludes, "Désormais, je serais plus indulgent!"

That this mechanism is the proximate cause of Volkmann's contracture is attested by the universal finding of segmentary arterial spasm in all cases in which the artery is surgically exposed during the acute stage. What could not be so easily demonstrated but must logically be considered a key factor is vasoconstriction of the collaterals when the resulting ischemia is total or nearly so. Arterectomy affords all the elements of completely rational treatment because it removes a segment of artery that is not contributing to the circulation but is a source of abnormal sensory impulses, and because it completely interrupts the sympathetic reflex arc both centrally and locally, and thereby most effectively produces vasodilatation of the collaterals.

#### CONCLUSIONS

Volkmann's ischemic contracture should be divorced from its association with supracondylar fracture of the humerus. It is the result of a nearly complete ischemia produced by arterial spasm of the main artery and the collateral circulation.

Interruption of the sympathetic reflex arc is the rational treatment.

Arterectomy gives the best results in stubborn cases.

520 Commonwealth Avenue

#### REFERENCES

1. Griffiths, D. L. Volkmann's ischaemic contracture. *Brit. J. Surg.* 28:239-260, 1940.
2. Hill, R. L., and Brooks, B. Volkmann's contracture in hemophilia. *Ann. Surg.* 103:444-449, 1936.
3. Leriche, R. Conditions dependent upon vasomotor changes in blood-vessels. In *Nelson New Loose-Leaf Surgery*. Vol. III. New York: Thomas Nelson & Sons. Pp. 779-832P.
4. Homans, J. *Circulatory Diseases of the Extremities*. 330 pp. New York: Macmillan Co., 1939.

- 5 *Idem* Personal communication
  - 6 Montgomery A H and Ireland J Traumatic segmentary arterial spasm *J A M A* 105 1741 1946 1935
  - 7 Gige M and Ochsenr A Prevention of ischemic gangrene following surgical operations upon major peripheral arteries by chemical section of cervicodorsal and lumbar sympathetics *Ann Surg* 112 938 1959 1940
  - 8 Hamoussi Cited by Foille J The physiological pathology of the arterial emboli of the extremities *Surgery* 3 309 1938
  - 9 Ierich R Fontaine R and Dupuytren S M Arterectomies with follow up studies on 78 operations *Surg Gynec & Obst* 64 149 1955 1937
  - 10 Luzuy M Contractions ischémiques par plaies en venon du membre supérieur Leur traitement par infiltration anesthésique du ganglion stellaire *Mém Acad de chir* 62 25 1940
  - 11 Mayot R La maladie de Volkmann (retraction ischémique de muscles les flexisseurs des doigts) Pathogénie Traitement *Rev d'orthop* 22 385 483 1935
  - 12 Leveuf J Des lésions provoquées par les troubles de la circulation capillaire consécutifs à la contusion de l'artère humérale dans les fractures supra condyliennes de l'humérus (soi disant syndrome de Volkmann) *J de chir* 51 177 214 1938
  - 13 Du Pan M Retraction ischémique de Volkmann guérie par arthrotomie de l'humérus *Rev méd de la Suisse Rom* 59 9 785 1939 1940
  - 14 Marmel M Discussion de Mayot R
  - 15 Browne W E The necessity for use of splints at certain stages in the treatment of infections of the hand with a demonstration of some of the newer types *New Eng J Med* 215 43 49 1936
- ADDITIONAL REFERENCES**
- Brooks B Pathologic changes in muscle as a result of disturbance in circulation *Arch Surg* 5 188 216 1922
- Brooks B Johnson G S, and Kirtley J A Jr Simultaneous venous ligation an experimental study of the effect of ligation of the common venous vein on the incidence of gangrene following arterial constriction *Surg Gynec & Obst* 59 496-500 1934
- Bruce J Localized Volkmann's contracture *J Bone & Joint Surg* 22 38 1940
- Dudgeon L S Volkmann's contracture *Lancet* 1 8 85 1902
- Fèvre and Bertrand, Boppe Roederer, Recamier Walther Perrot and Pouzet In discussion of Mayot R La maladie de Volkmann *Rev d'orthop* 22 695 734 1935
- Funck Brentano and Hepp J Le rôle du spasme dans le syndrome de Volkmann *Mém Acad de chir* 65 1291 1294 1939
- Garber, J. B. Volkmann's contracture as a complication of fractures of the forearm and elbow *J Bone & Joint Surg* 21 154 168 1939
- Girdlestone G R Treatment of fractures in the light of their ischaemic complications *J Bone & Joint Surg* 14 55 762 1932
- Griffiths D L Arterial embolism study of eight cases *Lancet* 2 1349 1344 1938
- Himsa G Unusual case of Volkmann's ischaemic contracture *Brit M J* 2 418 1937
- Horwitz T Ischaemic contracture of lower extremity *Arch Surg* 41 945 959 1940
- Jefferson G Arterial embolism *Brit M J* 2 1090 1094 1934
- Jepson P N Ischaemic contracture *Ann Surg* 84 785 795 1926
- Jones E D Volkmann's ischaemia observations at open operation *Brit M J* 1 1033 1940
- Jones R Volkmann's ischaemic contracture *Lancet* 2 798 1928
- Le Roque G P Ligation of the external iliac artery and vein above and below a common truncating bullet wound of the three vessels *Ann Surg* 73 265 284 1921
- Ierich R Les maladies des ligaments *Presse méd* 48 41 44 1940
- Littlewood H Volkmann's contracture *Lancet* 1 193 1902
- Leblond P and Munera G La rélicité du spasme artériel dans un syndrome de Volkmann *Mém Acad de chir* 65 53 755 1939
- Mistas R Some experiences and observations in the treatment of arterio-venous aneurisms by the intramuscular method of suture (endoaneurismorrhaphy) with special reference to the transverse route *Ann Surg* 71 403 427 1920
- Meyerding H W Volkmann's ischaemic contracture associated with supracondylar fracture of humerus *J A M A* 106 1139 1144 1936
- Meyerding H W and Krusen I H Treatment of Volkmann's ischaemic contracture *Ann Surg* 110 417 426 1939
- Middleton D S In discussion of Jones R
- Morcia F E G Volkmann's ischaemic contracture *Arch brasil de chir e ortopedia* 6 289 1938
- Morwood J B Two cases of supracondylar fracture of humerus with absent radial pulse *Brit M J* 1 1163 1939
- Murphy J B Myositis *J A M A* 63 1249 1255 1914
- Nelson H P A case of impending ischaemic contracture *Lancet* 2 795 1930
- Page H W Volkmann's ischaemic paralysis its treatment by tendon lengthening *Lancet* 1 83 85 1900
- Plewes L W Occlusion of brachial artery and Volkmann's ischaemic contracture *Brit M J* 1 1054 1940
- Pouzet F and LeClerc G Paralyse de Volkmann lésion constituée à la 70e heure *Lyon chir* 34 187 190 1937
- Riche V Aussous J and Geneste J Syndrome de Volkmann du membre inférieur *Presse méd* 47 1173 1175 1939
- Rouhier G and Bossou C Un cas de paralysie ischémique de Volkmann terminée par gangrène et amputation *Mém Acad de chir* 66 409 415 1940
- Thomas J J Nerve involvement in ischaemic paralysis and contracture of Volkmann *Ann Surg* 49 330 370 1909
- Uggeri C and Massone A La sintomatologia arteriale delle flebiti degli arti *Arch ital de chir* 49 429 4 9 1938
- Wilson P D Fractures and dislocations in relation of elbow *Surg Gynec & Obst* 56 335 359 1933

## CIRRHOSIS OF THE LIVER COMPLICATED BY PERSISTENT RIGHT HYDROTHORAX AND ASCITES

### Report of an Unusual Case

JOSEPH R. FROTHINGHAM, M.D.\*

BOSTON

FROM time to time, cases of cirrhosis of the liver complicated by right hydrothorax have been reported, but the case described below is unusual because of the huge amounts of fluid removed and the great number of tapings both pleural and peritoneal required during the course of the patient's illness. Christian<sup>1</sup> reported a case of hepatic cirrhosis with left-sided hydrothorax requiring a total of nine taps ranging from 800 to 2400 cc. for each tap. Goodman<sup>2</sup> described a case in which an accident had caused a diaphragmatic hernia and in which the extended omentum acted as a ball valve, causing "pleural ascites" in a patient with cirrhosis. Seven taps were necessary, with a total of 20,450 cc. removed. Individual taps yielded 650 to 5200 cc. Sears and Lord<sup>3</sup> described a case of ascites from which "dur-

ing the last two months of his [the patient's] life between sixty and seventy-two quarts were three times withdrawn." Clerc, Debray, Chassigne and Souillard<sup>4</sup> reported a case of long standing cirrhosis requiring one hundred and fourteen abdominal taps over a period of ten years. The frequent tapings and recurring ascites had caused a remarkable distortion of the abdomen. The amounts of fluid removed were not given.

Heart failure has long been recognized as a cause of right pleural effusion. Garvin<sup>5</sup> described such a case in which forty-five taps, averaging 1065 cc. each (total 47925 cc.), were required. For one period of nineteen days, a tap was necessary daily, each one yielding about 1000 cc. The most fluid removed at one time was 1850 cc.

There are many other causes for recurrent hydrothorax, but the case reported below is unusual because the number of taps and the amount of

\*Assistant in medicine Harvard Medical School, junior associate in medicine, Peter Bent Brigham Hospital, captain, Medical Corps, United States Army.

fluid removed far exceed any that I have been able to find in the literature. Even though permission for an autopsy was refused in this case, many diagnostic data, including biopsy, were obtained during the illness, so that the diagnosis is reasonably certain.

### CASE REPORT

H. L. D., a 40-year-old physician, had been in robust health about a year before his first hospital admission (November 4, 1939). At 14, the right hip had been incised and drained for a questionable tuberculosis. The patient had recovered from this satisfactorily. At 28, he had had several attacks of pain under the right costal margin, but none since. The past history was otherwise not remarkable. There was no history of excessive alcoholic intake, although the patient used whisky moderately. The family and marital histories were noncontributory.

For 10 months before admission, the patient had noticed a tendency toward easy fatigability but had no definite complaints. He complained of vague, mild abdominal discomfort, but there was no localized pain of any sort or jaundice at any time. During the 2 weeks before admission, he noted an increasing tendency to easy fatigue and a gradual enlargement of the abdomen, so that his trousers became uncomfortably tight. It was believed that ascites was present, and he entered a hospital for peritoneoscopy and further study. Examination of the blood and urine was negative. The blood Hinton reaction was negative. X-ray films of the abdomen and chest revealed no abnormalities, except for the characteristic abdominal haziness associated with the high diaphragms caused by the ascites. Peritoneoscopy showed "a tiny liver, the entire surface of which was made up of irregular clusters of small nodules"; no biopsy was performed. The patient was discharged on the following day, with a diagnosis of hepatic cirrhosis. The abdominal wound drained slightly for a few days and then entirely healed. The fluid in the abdomen thereafter seemed to decrease until none could be demonstrated. The patient remained at home leading a fairly sedentary life on a high-vitamin, high-carbohydrate regime, but in spite of this he noted increasing fatigue. He lost about 20 pounds in weight during the next 2 months.

On January 6, 1940, the patient noted marked increasing dyspnea, and on examination the following morning he was found to have a massive pleural effusion on the right. He again entered the hospital on January 7. Physical examination showed signs of fluid in the right chest, a barely palpable liver edge and slight icterus. The spleen was not felt. The urine and blood were normal. The serum protein was 7.8 gm. per 100 cc.; the albumin was 3.1 gm. and the globulin 4.7 gm. The benzoic acid (Quick) test showed decreased liver function; the icteric index was over 100. Two thousand two hundred cubic centimeters of straw-colored fluid was removed in two taps. Culture showed no growth. The fluid protein was 0.72 gm. per 100 cc. X-ray examination of the chest after removal of the fluid showed normal lung fields and no apparent cause for the fluid. The patient was discharged after 4 days.

On January 13, he was again admitted because of dyspnea caused by hydrothorax on the right. He remained in the hospital for 12 days, and was tapped 3 times, with the removal of 2400, 3800 and 3300 cc. of fluid. The fluid consistently showed a specific gravity of 1.010 to 1.012, and was of an amber color. No tumor

cells were found in the centrifuged sediment. There was a small amount of bile in the urine. At the patient's request, it was decided to perform any further tapplings at his home, and he was discharged after 12 days. There was still no evidence of accumulation of fluid in the abdomen.

From January 27 to March 1, a right thoracentesis was required every 2 days for relief of dyspnea. The smallest amount of fluid removed at one tap was 1600 cc.; the greatest amount at one time was 4100 cc. The tapping usually yielded 2800 to 3500 cc. Except for one gastrointestinal upset characterized by chills, fever and diarrhea for which he was hospitalized a few days and which subsided spontaneously, he was fairly comfortable when not bothered by dyspnea caused by the hydrothorax. When this was marked, the liver edge was easily palpated, and the edge of the spleen could occasionally be felt. Sediment from the fluid again showed no tumor cells on repeated sections. There were an abundance of eosinophils and mesothelial cells and a few leukocytes, which were interpreted as being a reaction to the frequent tapplings. The serum protein on February 7 was 6.1 gm. per 100 cc.; the albumin was 3.1 gm., and the globulin 4.7 gm. The icteric index was 15. The specific gravity of the chest fluid was usually recorded as 1.007 or less. Venous pressure in the right arm on March 8 was 75 mm. of water.

On March 11, the patient entered the Peter Ben Brigham Hospital for further study. Following complete removal of the fluid in the right chest, a bronchoscopy was passed. No abnormalities of the bronchial tree could be found in the lungs. X-ray studies of the lung following lipiodol injections likewise showed no abnormal findings. A swallow of barium revealed very marked varices at the lower end of the esophagus. There was no evidence of heart disease. Since these studies revealed no evidence of cancer in the pleura, mediastinum or lungs, it was believed that the recurrent right hydrothorax must be associated with the cirrhosis of the liver which had been proved by peritoneoscopy and reduced liver-function tests.

With the exception of 2 days during March, it was necessary to tap the right chest every day. The tapping yielded 1200 to 4100 cc. each, usually about 2400 cc. This meant that the patient was constantly accumulating at approximately 100 cc. per hour in the right chest. The left chest and abdomen remained free of fluid. There was no peripheral edema at this time. There were twenty-five consecutive daily taps.

During April and the first half of May, it was necessary to tap him only every 2 days. The decision to tap the chest was determined by the patient's discomfort. The amount of fluid removed usually averaged around 2800 to 3000 cc. His general condition remained essentially unchanged. During the latter part of May and early part of June, he was tapped every day or every 2 days. From June 16 to July 30, taps were performed daily. The patient was not tapped on July 31. From August 1 to September 30, he was tapped daily. Thus, with the exception of 1 day, the patient required daily right thoracenteses for 106 consecutive days. Most of these procedures were done in the home, but during the latter part of August and in early September the patient felt well enough to travel by automobile to the hospital for the daily chest tap. A total of 1500 to 2500 cc. was the usual yield of each tap.

Because of the apparently endless flow of fluid into the chest and because generalized anasarca was beginning to develop, he was again admitted to the Faulkner Hospital on September 12. On July 12, the serum protein

had been 48 gm per 100 cc with an albumin of 2.4 gm and a globulin of 2.4 gm. On September 17 the serum protein was 6.3 gm per 100 cc, the albumin was 2.6 gm and the globulin 3.7 gm. Since the patient was quite obviously not improving further steps were deemed advisable, to stop the recurring right hydrothorax. It was reasoned that following the removal of 2000 to 3000 cc of fluid from a closed structure such as the chest where there is normally a pressure less than atmospheric there must be an increase in negative pressure. This partial vacuum would tend to suck even more fluid into the pleural space. If, therefore, the fluid were replaced by as much air as necessary to bring the pressures to nearly neutral there would be less tendency for the fluid to reaccumulate in the right chest. Therefore during the next few thoracenteses, approximately the volume of about half the total fluid removed was replaced in the form of air. After this procedure had been repeated about five times, the amount of fluid began to decrease. Associated with this, there was some slight pain on deep breathing on the right side and there was a slight rise in temperature to a maximum of 100.4°F. This gradually subsided. A slight right pleural friction rub was associated with the pain and fever. The amount of fluid aspirated from the chest gradually diminished until on October 7 only 350 cc was removed. Complete removal of the fluid resulted in pleuritic pain, and therefore, a cushion of fluid was left after each tap. This was the last chest tap that was necessary for 4½ months.

The patient was once more discharged home at his own request, and his condition remained essentially unchanged for the next 4 days. However he soon began to notice some swelling of the abdomen and on October 13 his first abdominal paracentesis yielded 5000 cc of straw-colored fluid, which did not clot on standing. The abdominal fluid appeared to be entirely similar to the chest fluid that had previously been obtained. The specific gravity was low, as was the protein content of the fluid.

During the next 2½ months, it was necessary to perform abdominal paracenteses about every 4 to 6 days, to relieve the patient's discomfort. 2000 to 4000 cc was the average yield of each tap. During January 1941 it was necessary to tap the abdomen every other day.

On January 18 the patient was admitted to the Faulkner Hospital for an omentopexy and ligation of the splenic artery. This was undertaken because he had become discouraged with his long illness and because the accumulation of fluid seemed to be rapid. At operation no adhesions were found in the abdomen or about the spleen. The liver appeared normal in size, and the surface was extremely hard and covered with very many bluish nodules. A biopsy of the liver showed microscopically numerous broad, fibrous trabeculations separating the liver substance into irregular lobes. Wherever the portal structures could be identified there was always a broad connective-tissue zone and in addition, an irregularly distributed fibrosis throughout the structure. Definite hyalinization was not found, although there were some areas suggestive of it. The pathologist's diagnosis was cirrhosis of the liver to be regarded as unclassified although suggesting Laennec's type. Because of technical difficulties and the large spleen without adhesions, the splenic artery was not tied. The omentopexy was completed and the abdomen closed without drainage. Eight paracenteses were required while the patient was in the hospital after the operation. He returned home on February 11.

At home it was necessary to tap the abdomen every day or every other day (1500 to 2000 cc each tap) until February 27 when the patient complained of dyspnea and

discomfort in the right chest. Because of the markedly thickened pleura from the previous thoracenteses, it had for several months been nearly impossible to determine the presence or absence of fluid in the chest. However, a chest tap revealed 3000 cc of the usual straw-colored fluid. During the next 4 days daily chest taps revealed a gradually diminishing accumulation of fluid in the right thorax. The abdomen had to be tapped only once during this time, and only 700 cc of fluid was removed. However, with the cessation of the fluid in the right pleural cavity, abdominal paracenteses again had to be resumed every 2 to 4 days. Usually, 2500 to 3500 cc of fluid was removed with each tap. More fluid in the abdomen caused great discomfort. Profuse draining often occurred following abdominal taps and the patient occasionally leaked freely enough through the wound to make tapping unnecessary for an extra day. His condition continued about the same until the end of April. On one occasion in April he again complained of discomfort in the right chest. A thoracentesis yielded about 100 cc of grossly purulent material. A stained smear showed this material to contain innumerable leukocytes and a few staphylococci and streptococci which may have been contaminations no culture was taken. The patient showed little clinical evidence of empyema and it was not necessary to tap the chest again.

During the course of the illness, the urinary output was quite scanty. On examination the urine was usually highly concentrated but otherwise not remarkable. Various diuretics of the mercurial and xanthine derivatives were tried without effect. During March, April and May, 1941, increasing edema of the lower limbs and abdominal wall gradually developed. About April 15, the patient began to notice some ecchymoses of the skin of the legs and trunk. There was also some transient pain in many of the small joints of the body. A few days later, the urine became a muddy wine color, and gross hematuria was noted. The urinary sediment contained many red and white blood cells, and remained so for the duration of the illness.

The course was steadily downhill from then on. Abdominal taps were required every 2 or 3 days. The amount of fluid removed ranged between 600 and 3400 cc. The patient was often very insistent on being tapped, even though it seemed unnecessary at the time. The omentopexy had apparently failed to benefit him.

On May 29, he gradually lapsed into a comatose state, and died on June 1.

#### SUMMARY

A case of cirrhosis of the liver, proved by biopsy and without any clinically demonstrable pathology of the lungs, mediastinum, pleura or heart, is reported, recurrent right hydrothorax necessitated two hundred and eleven thoracenteses for the removal of a total of 467,100 cc of fluid from the right chest. In addition, it was necessary to perform eighty-seven abdominal paracenteses for the removal of a total of 214,580 cc of ascitic fluid. The ascitic fluid and the chest fluid appeared to be similar. With the exception of one day, it was necessary to tap the chest daily for one hundred and six consecutive days. The greatest amount of fluid removed from the chest at any one time was 4100 cc.

1153 Centre Street  
Jamaica Plain



## REFERENCES

1. Christian, H. A. Bloody pleural fluid, an unusual complication of cirrhosis of the liver. *Ann. Int. Med.* 10:1621-1623, 1937.
2. Goodman, S. "Pleural ascites": the result of traumatic rupture of the diaphragm in a case of latent hepatic cirrhosis. *J. A M A* 109:1980-1982, 1937.
3. Sears, G. G., and Lord, F. T. The symptoms and treatment of hepatic cirrhosis in the light of seventy-eight autopsies. *Boston M. & S. J.* 147:285-289, 1902.
4. Clerc, Debray, Chassagne, and Soullard. Déformation extrême de l'abdomen, après ponctions répétées, au cours d'une cirrhose avec ascite. *Bull. et mém. Soc. méd. d. hôp. de Paris* 55:1128-1130, 1939.
5. Garvin, C. F. Right-sided pleural effusion in heart failure: report of an unusual case. *Am. Heart J.* 16:501-504, 1938.

## ARGYRIA CONFUSED WITH HEART DISEASE\*

SAMUEL A. LEVINE, M.D.,† AND JASPER A. SMITH, M.D.‡

BOSTON

CYANOSIS is a common finding in both congenital and acquired heart disease. When marked, it is detectable not only in the skin (especially in the most distal parts of the body such as the hands, feet, ears and nose), but also in the mucous membranes and the tongue. Argyria also produces a discoloration of the skin, resulting in a slatelike appearance that may closely resemble the cyanosis of heart disease. Our attention was called to the confusion between these two states by the mistaken diagnoses that were made on several occasions in the last few years. It is evident that the error of overlooking argyria and misinterpreting the discoloration of the skin as being due to the cyanosis of heart disease is a grave one but easily avoidable. Furthermore, the gradual and insidious development of argyria itself is a condition that is entirely unnecessary and preventable. It is because of these simple facts that we believe it appropriate to report the cases discussed below.

It is not our purpose to review the literature on argyria or to go into the mechanism or chemical background of its development. Because of the apparent harmlessness of even marked degrees of argyria, the great majority of cases are never reported. All physicians at one time or another have seen cases, so that the sparse statistical reviews in medical journals can give only a meager picture of its prevalence. We were able to find only one reference in the recent literature in which the presence of argyria led to the mistaken diagnosis of heart disease.<sup>1</sup>

The discoloration in argyria may be of two types: local, such as that around the eyes due to instillation of various forms of silver solutions into the lachrymal ducts, and generalized discoloration of the skin. The latter is apt to result from the absorption of silver through the nasal and gastrointestinal mucosa, such as that following

nasal instillations, or by the injection of silver arsphenamine in the course of antisyphilitic therapy. Gaul and Staud<sup>2</sup> point out that the degree of discoloration depends directly on the extent and duration of the solar or artificial radiation and the amount of silver present in the skin. In following patients receiving antisyphilitic therapy, the authors believed that the clinical detection of argyria occurred when a total of about 8.0 gm. of silver arsphenamine had been given parenterally. It is well known that parts of the body exposed to the light are more profoundly discolored than areas protected by clothing. It is also of interest that the regional intradermal injection of a solution containing 1 per cent potassium ferrocyanide and 6 per cent sodium thiosulfate produces a local and permanent disappearance of the slatelike skin discoloration.<sup>3</sup> In fact, this procedure has occasionally been used therapeutically. The discoloration from bismuth may closely resemble that from silver, but the former is prone to recede spontaneously in three to six months, whereas the latter remains unchanged indefinitely.<sup>4</sup>

## CASE REPORTS

CASE 1. A 7-year-old boy was brought in for examination on January 5, 1934, with the diagnosis of congenital heart disease. He was supposed to have had a bluish discoloration of the skin, especially around the nose and lips, since birth and was treated all this time as a case of congenital heart disease. His father stated that the skin of the rest of the body appeared normal until a few months prior to the visit, and since then the discoloration had involved the entire body. The child otherwise felt well, went to school and played normally, except that he grew fatigued more easily than other children. The pediatrician had always cautioned the parents about the child's activities, and the entire household lived under the constant dread that organic heart disease entailed.

Physical and x-ray examinations revealed a heart of normal size. There was a Grade I apical and basal systolic murmur, but no other abnormalities. Electrocardiograms were normal. The general state of nutrition was only fair, and the urine was entirely normal. There was no clubbing of the fingers. The important finding was the diffuse grayish-blue line of the skin, most marked in the face, but moderate in degree over the rest of the body.

\*From the Medical Service, Peter Bent Brigham Hospital, and the Department of Medicine, Harvard Medical School.

†Assistant professor of medicine, Harvard Medical School, physician, Peter Bent Brigham Hospital.

‡First Lieutenant, Medical Corps, United States Army, Camp Edwards, Falmouth, Massachusetts, formerly, volunteer assistant, Medical Service, Peter Bent Brigham Hospital.

It was this discoloration that had been interpreted as cyanosis and had led to the diagnosis of congenital heart disease. It quickly became evident that the color was quite different from what is seen in organic heart disease. Furthermore, the mucous membranes of the tongue, mouth and conjunctiva appeared normal, if the high degree of discoloration had been due to congenital cardiac cyanosis, one would certainly have expected to find evidence of it in these structures. At this point, on direct questioning of the father, it was learned that since the age of 3 months when the child had a slight nasal cold he had been given almost daily instillations of silver nitrate or Argyrol in the form of drops or spray to prevent sinus infection. In November, 1933, he had been given a half dropperful of silver nitrate solution in each nostril three times a day for a week, and off and on ever since. During the 1st year or so of this silver treatment, the mother was carrying out the doctor's orders. Subsequently, it was more or less her own method of prophylaxis that motivated treatment. However, she had never been told about the potential danger, or to stop the nose drops.

The entire situation was explained to the family and it was made clear that the heart was perfectly normal and that the boy should never use silver in any form again. He has been well ever since, although he continues to show the marked bluish discoloration of the skin.

**CASE 2.** A 15-year-old girl was seen on April 5, 1941 because of a general run down condition, rapid pulse, loss of weight and slight fever of several months duration. Although the physician in charge was not greatly concerned about the situation, there was some suspicion of the possibility of a smoldering rheumatic fever or subacute bacterial endocarditis. She had been seen by numerous physicians because of recurrent slight grippelike infections and a general feeling of asthenia. Many tests, including blood cultures, urinalyses and chemical analyses of the blood, were normal, and x-ray studies were negative. The basal metabolic rate was found to be -18 per cent, and for this reason 1 gr. of thyroid was given three times daily. This was discontinued after a few weeks. More recently, the patient had had a mild sore throat, bilateral otitis media requiring paracentesis, and slight cervical adenitis. Most of the symptoms subsided, although she tended to run a temperature slightly over 99°F. At various times during these few months, attempts were made to have the child get out of bed and resume moderate activities. Each time, the mother and a physician noted that after a little play the pulse would be rapid and what was interpreted as a cyanotic tint to the skin appeared.

Examination revealed a tall, thin, attractive looking girl with a very faint bluish tint to the skin of the face. The heart was entirely normal, except for a very faint apical systolic murmur.

It quickly became apparent that the main problem was a psychiatric one and involved a difficult relation between mother and daughter. Because of the suspicious appearance of the skin, a direct inquiry was made concerning the use of nose drops. It was then learned that for 5 or 6 years the girl had received almost daily instillations of silver nitrate solution. The mother admitted using about 2 or 3 ounces of such solution a year. This had been unsuccessful in preventing colds and sinus infections to which the patient was subject.

When the entire situation was explained to the mother and the family physician, their apprehension concerning the so-called cyanosis was relieved. The importance of the physical aspects of the problem was minimized, and after an appropriate conversation with the child and the mother a better psychologic adjustment was obtained.

The result was that the child resumed her schooling and returned to good health. In this case the disfigurement from the argyria was almost nil, since it could hardly be detected. Its recognition, however, prevented an irretrievable injury to a young girl whose future would otherwise have been greatly handicapped.

**CASE 3.** A 37-year-old woman was seen on March 23, 1938. She complained that she had no pep and that her fingers were blue. She had had both rheumatic fever and chorea in childhood, and during the last several months had noticed that her heart turned over at times. She had been put to bed by her physician because it was thought that she had heart disease. There was no history of dyspnea or pain in the chest.

Examination showed a tall, thin woman with a somewhat slate-like discoloration of the face. The heart was not enlarged, but there was a slight apical systolic murmur. The blood pressure was 134/85. Aside from the murmur, nothing abnormal was found except that the fingers were distinctly blue. Electrocardiographic tracings were normal, and the vital capacity of the lungs was 3400 cc.

It was obvious that this patient had no organic heart disease. The discoloration of the skin was of the type seen in argyria, and with this in mind it was learned on direct questioning that for the previous 5 years she had taken seven drops of a 10 per cent Neosilvol preparation in each nostril every night. This procedure had been carried out on the advice of a nose and throat specialist because of chronic sinus infection.

In this case, the correct interpretation of what the physician regarded as cyanosis led to the diagnosis of no organic heart disease, despite the past history of rheumatic infection.

**CASE 4.** A 50-year-old woman was seen on February 3, 1939, complaining of weak spells with peculiar sensations in the chest, and a feeling as if the blood were rushing to her head. There was no dyspnea or difficulty on walking, and no history of previous rheumatic infection.

Examination revealed a faint grayish blue tint to the skin of the face, and a distinctly bluish discoloration of the base of the nails. The blood pressure was 135/88, the heart was not enlarged, there were occasional extra systoles, and the first sound at the apex and the second sound in the pulmonary area were accentuated. There was a definite, but very short, presystolic murmur at the apex. The vital capacity was 1900 cc., and the electrocardiogram showed a prominent auricular complex, or P wave. The remainder of the examination was entirely negative.

The appearance of the skin aroused the suspicion of argyria, and on further questioning, it was learned that for 4 years the patient had been using a Neosilvol spray twice daily. She stated that she squeezed the bulb of the atomizer four times into each nostril with each treatment. Immediate and complete discontinuance of all silver medication was urged.

In this case, there was evidence of well compensated organic heart disease, but the detection of argyria helped to minimize the gravity of the situation, for there was no evidence of heart failure.

**CASE 5.** A 72-year-old physician was seen on August 7, 1940. During the previous several months, he had noticed increasing shortness of breath, swelling of the ankles and spells of discomfort in the mid-sternum on hurrying.

Examination showed a blood pressure of 185/85, slight enlargement of the heart and a coupled beat, but there were no murmurs. There were a few rales at the right base and considerable soft, pitting edema of the legs. Electrocardiographic tracings showed delayed conduction

time (PR interval, 0.24 second) and coupled beats due to extrasystoles. There was marked slate-like discoloration of the face, but the scleras were not involved.

This patient had congestive heart failure on a basis of coronary-artery sclerosis and slight hypertension. However, the discoloration of the skin was obviously due to argyria, and it was learned that 20 years previously he had begun using nose drops containing either silver nitrate or Argyrol. He continued this more or less regularly for 10 years, but did not notice the change in the skin until a few years after the instillations had been discontinued.

The heart failure progressed despite appropriate treatment, and the patient died in March, 1941. In this case, the marked argyria was an incidental finding, and had no effect on the cause or prognosis of the basic organic heart disease.

### DISCUSSION

In these 5 cases of argyria, mistakes in diagnosis or interpretation of so-called "cyanosis" had previously been made. In 4 cases, faint or marked discoloration of the face or fingers had been regarded as cyanosis of circulatory origin. In all but 1, the fact that nose drops of silver preparations had been used for long periods had been entirely overlooked by the physicians in charge, and had not been mentioned by the patients or their families until direct inquiry was made. In 1 case, the marked slate-like tint, which had been present since infancy, was interpreted as cyanosis of congenital heart disease. In 2 other cases, a milder bluish tinge of the skin brought up suspicions of acquired heart disease. In none of these 3 cases was any evidence of organic heart disease detectable. Of the 2 remaining cases, one patient had a slight, well-compensated mitral stenosis, and the other, heart failure on the basis of hypertension and coronary-artery sclerosis; in both, the "cyanosis" was due entirely to argyria.

It can be readily seen from these experiences that argyria is quite common and often overlooked. It is essential to recognize this fact to avoid serious errors in diagnosis and prognosis. Argyria can naturally be present either with or without organic heart disease. There seems to be no physical handicap that results from even marked argyria, but very great harm can be done to the psyche and personality of the patient from the cosmetic discoloration of the skin. When argyria accompanies organic heart disease, the prognosis is obviously a good deal better than if the condition is misinterpreted as cardiac cyanosis.

No doubt, there is some advantage in using silver preparations for short periods. However, there appears to be no reason to continue the use of nose drops containing silver over the course of months or years when it is realized that the insidious onset of an irreversible and ugly discoloration of the skin may result. Patients and their families should be cautioned very carefully against this danger. It might even be wise to write the expression "do not refill" on all prescriptions containing silver salts.

### SUMMARY AND CONCLUSIONS

Five cases of argyria are presented in which the condition was entirely overlooked for months or years, and the discoloration was misinterpreted as definite or possible evidence of organic heart disease. In one case, it was so marked since infancy that the child was treated for many years as a patient suffering from congenital heart disease. In another, because of bizarre symptoms and slight fever, the possibilities of smoldering and active rheumatic fever or subacute bacterial endocarditis were considered. In another case, because of the past history of rheumatic fever, the possibility of rheumatic heart disease had been entertained. The remaining patients had organic heart disease, but the so-called "cyanosis" was not due to heart failure.

Argyria must be distinguished from the cyanosis of heart or pulmonary disease. It has a peculiar, grayish, slate-like tint, in contrast to the purplish hue of cardiac cyanosis. It is most frequently confined to the parts of the skin exposed to light, the tongue and mucous membranes, which are generally involved in cyanosis due to circulatory disease, being unaffected.

It is evident that argyria is not uncommon, and if it is not recognized, it may lead to a serious error in the diagnosis or management of heart disease or both. Finally, because it is an unnecessary and preventable handicap that is insidious in its development, greater caution must be exercised by physicians in dispensing silver preparations.

### REFERENCES

1. Royster, L. T. Argyria: report of a case in a patient aged five and a half years. *J. Pediat.* 1:736-738, 1932.
2. Gaul, L. E., and Staud, A. H. Clinical spectroscopy. *J. A. M. A.* 104:1387-1390, 1935.
3. Stillians, A. W. Argyria. *Arch. Dermat. & Syph.* 35:67-77, 1937.
4. Spiegel, L. A discoloration of the skin and mucous membranes resembling argyria, following the use of bismuth and silver arsenite-amine. *Arch. Dermat. & Syph.* 23:266-286, 1931.

## HEMOTHORAX COMPLICATED BY INFECTION WITH *CLOSTRIDIUM WELCHII*\*

JOSEPH P. LYNCH, MD,<sup>†</sup> AND JOHN W. STRIEDER, MD<sup>‡</sup>

BOSTON

WITH the increasing mechanization of modern life, the occurrence of hemothorax and hemopneumothorax resulting from penetrating and nonpenetrating injuries has become so frequent that the conditions are usually sought for and recognized. Moreover, the possibility of infection as a complication of these injuries is generally appreciated, and when it occurs, measures are taken to deal with it. However, infection of a hemothorax by the gas producing micro organisms is a complication not frequently described in civil practice, most of the reported cases having occurred as war injuries. Such infections may be overlooked or the symptoms misinterpreted, since the production of gas by these micro organisms in the hemothorax may simulate hemopneumothorax, with a small but constant bronchopleural fistula

It is the purpose of this paper to discuss this complication of penetrating wounds of the thorax and to report our experience with such a case at the Boston City Hospital

That the condition is rare is apparent from the literature, for various reviews<sup>1, 2</sup> of infection with *Clostridium welchii* do not mention pleural involvement. Others<sup>3, 4</sup> mention it briefly, citing a single case, without further discussion. Elliott and Henry<sup>5</sup> analyzed their findings in an excellent review of 87 cases in World War I. They found that under war conditions 25 per cent of all hemothoraxes became infected, and 44 per cent of these were infected by the gas-producing bacilli. Hence 10 per cent of all hemothoraxes were infected by gas producing bacilli, and 33 per cent of these were fatal. The diagnosis is made by culture and smear of the aspirated fluid, although an odor of hydrogen sulfide may be accepted as very suggestive without the culture. Because the infection may remain localized in one part of the blood clot, a negative culture is some times obtained, therefore, repeated thoracenteses should be done in any suspicious case. Clinically, for the first twenty four to forty eight hours, these patients present a picture of a mildly infected hemothorax, the temperature is usually no more

elevated than that in a simple uninfected hemothorax, but the pulse is rapid beyond expectation.

The cases observed by these authors may be divided into five main types, depending on the predominance of gas production or toxicity: the acute pneumothorax, with overwhelming gas production, which appears clinically as a sudden tension pneumothorax with or without hemorrhage and may progress to a fatality in two or three days; the fulminating septic, in which delirium and jaundice are outstanding and which may be fatal in two or three days; the progressive pneumothorax, whose main feature is a free or localized collection of gas, symptoms and signs becoming obvious after the fourth or fifth day following injury; the progressive toxic, in which symptoms become apparent at the same time as those of the progressive pneumothorax and in which jaundice, restlessness and delirium are prominent, and the chronic, which progresses in the same manner as the usual infected hemothorax, without marked gas formation or toxemia

In treating such infections, these authors have found that radical surgery is most successful. Attempts to avoid opening the thorax proved largely unsuccessful probably because the large masses of infected clot were not removed. Some patients may do well with closed drainage, or the maneuver may be needed as a temporary measure to decompress those suffering severe mechanical disturbances or those who are markedly toxic; as a general rule, however, the open operation is advised

In a brief discussion of this condition, the reports of the Medical Department of the United States Army<sup>6</sup> ambiguously state that "open drainage was generally held to offer the best chance of recovery from this type of pleuritis, though closed drainage would have been more efficacious"

Two other reports of *Cl. welchii* infection of the pleura were found. Bider and Muller<sup>7</sup> report a case in which the infecting organism was introduced at the time of thoracentesis, a method of infection that they consider not uncommon. In the cases reported by these authors, this seems reasonable, but from our experience at the Boston City Hospital we cannot concur in their opinion concerning frequency. They believe that the opening of the pleural cavity and the resulting aeration

\*From the Second Surgical Service, Boston City Hospital

<sup>†</sup>Formerly resident surgeon, Second Surgical Service, Boston City Hospital

<sup>‡</sup>Instructor in thoracic surgery, Boston University School of Medicine; assistant in surgery, Harvard Medical School; associate surgeon for thoracic surgery, Boston City Hospital; visiting surgeon in charge of thoracic surgery, Massachusetts Memorial Hospital

are the most valuable features in the treatment. Porzecanski and Franchi,<sup>8</sup> report a case following a gunshot wound of the chest, in which the patient was treated by rib resection and recovered.

At the Boston City Hospital, many cases of penetrating wounds of the chest are admitted annually, yet this complication has been seen but twice in recent years. On one occasion, a patient with a stab wound of the chest showed *Cl. welchii* in the first culture of the hemothorax fluid two days after the injury. However, he failed to show signs of infection, subsequent cultures of the fluid were negative, and recovery was uneventful. The second case is presented in detail because it showed definite infection of the hemothorax by *Cl. welchii*, with recovery following early open drainage, after the method described by Dolley and Jones<sup>9</sup> for treatment of putrid empyema secondary to rupture of a lung abscess.

### CASE REPORT

T. L. (B. C. H. 1006093), a 34-year-old man, was admitted to the hospital on November 25, 1940, with the complaint of shortness of breath of 2 days' duration. He stated that 5 days before admission he was stopped on the street by two men, who, having been refused money, stabbed him in the left chest. The wound seemed superficial, and he cared for it at home with the help of his wife, who was a trained nurse. He was able to work as a tailor, although 2 days before admission he was moderately dyspneic. This symptom increased until the day before admission, when it was severe enough to keep him in bed. Despite bed rest, the dyspnea increased, and he entered the hospital.

On admission, the patient was acutely ill, anxious, moderately cyanotic and markedly dyspneic. The extremities were cold and moist, the pulse was 120, the temperature was 98°F., and the respirations were 38. The blood pressure was 145/90 and paradoxical between 145 and 120. To the left of the sternum in the 2nd interspace, there was a 2.5-cm. laceration, which grossly appeared clean and through which there was no exchange of air. The trachea was deviated far to the right, and the apex impulse was just to the left of the sternum. There was flatness over the lower two thirds of the left chest, with tympany above this. The breath sounds and tactile and vocal fremitus were absent over the entire left side. Otherwise, the physical examination was negative. The white-cell count was 42,000, and the red-cell count was 4,640,000 with a hemoglobin of 85 per cent. The urine contained many red blood cells and had 3 or 4 white cells per high-power field. The impression on admission was that of a left hemothorax with tension.

A thoracentesis was performed immediately, and 1200 cc. of red, odorless blood removed. Following this, the patient felt much better, the pulse was slower and stronger, and breathing was easier. A specimen of the blood from the chest was sent for a routine culture. For 24 hours, the patient was more comfortable, following the administration of oxygen, morphine and a transfusion of 500 cc. of citrated blood. After this interval, however, he slowly relapsed. The displaced mediastinum, which had come back considerably after the first thoracentesis, was again far to the right, the patient was dyspneic and anxious,

and the pulse ranged between 120 and 130, the temperature varying between 101°F. and normal. During the 2nd day, the patient had repeated slight chills lasting from 5 to 10 minutes and associated with increased anxiety, but no marked rise in the temperature. Blood cultures taken during two of the chills were negative. About 60 hours after admission, the patient's condition seemed as poor as when he was first observed, and thoracentesis was performed again. This time, the fluid was thinner, of a chocolate color, and had a definite odor of hydrogen sulfide. About 1500 cc. was withdrawn, with immediate improvement; the pulse was stronger, the respirations easier, and there were no more chills. In addition, a moderate amount of gas was withdrawn with the changed blood, which had the same foul odor.

A smear of the fluid was made at once, and many large gram-positive bacilli were seen. Investigation of the fluid sent for culture on the day of admission showed that a large gram-positive bacillus had grown anaerobically, and nothing had grown aerobically. This bacillus showed all the characteristics of *Cl. welchii*.

On this evidence, the patient was taken to the operating room, and under local anesthesia a 10-cm. segment of the 8th rib was resected. Before the pleura was opened, the patient was given oxygen by a closed mask, and a small amount of positive pressure was maintained. The pleura was opened for about 2 cm., and the aspirating tip inserted. About 2000 cc. of foul-smelling old blood, together with many clots, was withdrawn. The pleura was then opened the entire length of the incision, a previously prepared large dressing was applied, and the patient was quickly turned on his back. There was very little sucking during this procedure, and none once the patient was on his back. He was returned to the ward in good condition; the respirations were much easier, and the pulse slowed to 100. He was transfused again, started on sulfanilamide, and given *Cl. welchii* antitoxin. He received 120 gr. of sulfanilamide a day for the first 3 days, and then 90 gr. daily was given for 7 days. During the first 3 days, 100,000 units of antitoxin, as well as intravenous fluids and nasal oxygen, was given. After this, the temperature was normal, and the pulse was 90.

The first dressing was done on the 3rd day, with the patient breathing against positive pressure. There was an obviously shifting mediastinum, and much foul discharge on the dressing. A culture was again positive for *Cl. welchii*. This was repeated on the 5th day, when the discharge was gray and foul. On the 7th day, the mediastinum was fairly well fixed, and a catheter was brought out through the dressing for irrigations, with maintenance of the closed wound by the dressing. On the 9th day, the fixation was sufficient to allow the insertion of large drainage tubes and the use of open irrigations. After 2 days, the foul odor had disappeared, and the drainage was serofibrinous. For irrigations, physiologic saline solution and, later, Dakin's solution were employed. On the 15th postoperative day, a culture of the drainage from the pleural cavity was negative for *Cl. welchii*, and they remained negative on all of several subsequent occasions.

The patient had one episode of right-sided chest pain, with an elevation of the temperature to 101°F. This lasted for 4 days and then disappeared. During this time, there were no clinical signs on the right, and a roentgenogram of the chest showed no abnormality on the right. Apart from this, the course was uneventful.

The patient was allowed up on the 32nd day, and was discharged on the 39th day, with a residual empyema cavity of 20 cc. Two and a half weeks following dis-

charge, the wound was completely healed, and the patient had returned to work.

### DISCUSSION

As penetrating wounds of the chest become commoner in civil life, one may expect to see this complication more frequently, and when such injuries occur in military practice the incidence will certainly be greater. Because fresh blood is not a favorable culture medium for *Cl. welchii*, few cases present signs and symptoms of infection within the first twenty-four hours. As the blood ages, however, it becomes an ideal culture medium, and a patient with a chest injury who is apparently doing well may become acutely ill within twenty-four hours. The production of gas by the infecting organism may lead one to believe that he is dealing with a pneumothorax incident to a small perforation, and thus valuable time will be lost if a course of watchful waiting is pursued.

All who have written on this subject, with one exception,<sup>6</sup> agree that the best treatment is early and complete removal of the old blood and clots from the chest by open drainage. Sulfanilamide, x-ray therapy and the specific antitoxin are undoubtedly of benefit, but it is our impression from this case, and from many other cases of anaerobic infection of the pleura,<sup>11</sup> that the aeration accompanying radical open drainage of the infected pleura is of paramount value. The dangers of widely opening, and permitting to remain open, the pleural cavity without adequate mediastinal fixation are appreciated by all thoracic surgeons; however, early open drainage may be necessary as a lifesaving measure and may be performed safely

in these cases by the use of the technic described above. Resection of a long length of dependent rib allows complete drainage of the pleural space, and the large dressing obviates too rapid an exchange of air and the resultant mediastinal flutter. Once the mediastinum is fixed, the treatment is that usually given postpneumonic empyema with open drainage.

### SUMMARY AND CONCLUSIONS

A case of hemothorax complicated by infection with *Clostridium welchii* is presented.

A review of the literature reveals that such a complication is rare in civil practice, but common in the surgery of war injuries.

From the cases reported, and from our experience with this case, we believe that early open drainage is the treatment of choice, but that it should be supplemented with specific antitoxin, chemotherapy and x-radiation.

### REFERENCES

1. Elison, E. L., Erb, W. H., and Gilbert, P. D. The *Clostridium welchii* and associated organisms. *Surg., Gynec. & Obst.* 64:1005-1014, 1937.
2. Ghormley, R. K. Gas gangrene and gas infections. *J. Bone & Joint Surg.* 17:907-915, 1935.
3. Weintrob, M., and Messeloff, C. R. Gas gangrene in civil practice. *Am. J. M. Sc.* 174:801-819, 1927.
4. Millar, W. M. Gas gangrene in civil life. *Surg., Gynec. & Obst.* 54:232-238, 1932.
5. Elliott, T. R., and Henry, H. Infection of haemothorax by anaerobic gas producing bacilli. *Brit. M. J.* 1:413-418, 1917.
6. The Medical Department of the United States Army in the World War. Wounds of the chest. Vol. VI, Part 1. Pp. 342-442. Washington: Government Printing Office, 1927.
7. Bader, R. E., and Müller, E. Gasbrandbazilleninfiziertes pleuraempyem. *München med. Wchnschr.* 86:1807, 1939.
8. Porzecanski, B., and Franchi, E. Un caso de pnoneumotorax simple, por *Clostridium perfringens*. *Arch. urug. de med., cir. y especialid.* 8:330-337, 1936.
9. Doley, F. S., and Jones, J. C. Treatment of acute suppurative pleuritis following rupture of a lung abscess. *J. Thoracic Surg.* 7:463-470, 1938.
10. Nelson, Louis Leaf. *Living Surgery: Surgery of the pleura*. Vol. IV. Pp. 499-530. New York: Thomas Nelson & Sons, P. 503A.
11. Strieder, J. W., and Lynch, J. P. Unpublished data.

## MEDICAL PROGRESS

### THE CHEMICAL MEASUREMENT AND CONTROL OF CLINICAL VITAMIN DEFICIENCY\* (Concluded)

WILLIAM T. SALTER, M.D.†

NEW HAVEN, CONNECTICUT

#### NICOTINIC ACID (NIACIN)

THE occurrence of nicotinic acid in concentrates derived from yeast was reported by Funk over a generation ago. Physiologic interest in the vitamin began when Warburg and Christian<sup>65</sup> found nicotinic acid amide as one of the split products of so-called "coenzyme II." Since then, increasing evidence that this substance is essential in enzyme systems having to do with oxidation in tissues has appeared. It occurs in both coenzyme I and coenzyme II, which participate in several well-defined biologic systems concerned with cellular oxidation. When Elvehjem et al.<sup>66</sup> showed that this substance cured black tongue in dogs and later isolated nicotinic acid amide from concentrates of liver extract, its value in clinical disease soon became apparent. Spies, Bean and Ashe<sup>67</sup> have reviewed the role of this vitamin in the treatment of pellagra and associated deficiencies. The material is even essential for bacteria, as shown by several investigators, including Mueller,<sup>68</sup> who worked with the diphtheria bacillus. Because its biochemical function has been known for some time, it is not surprising that chemical determination of this vitamin is well established.

Since this material is necessary for the synthesis of coenzymes I and II, it is apparent that a large amount must exist in tissues and in blood in the combined form as a coenzyme. Of the two factors, coenzyme I, otherwise known as cozymase, is the more easily estimated. Accordingly, studies of this material in blood usually relate to the content of coenzyme I in the erythrocytes. For example, Axelrod, Gordon and Elvehjem<sup>69</sup> showed that soon after large amounts of nicotinic acid were fed to mammals an increase in the coenzyme I (cozymase) content of the erythrocytes took place.

#### *Coenzyme I in Blood and Tissues*

Since certain yeasts specifically require coenzyme I for fermentation, this method of assay has been

Reprints of articles in this series are not available for distribution, but the articles will be published in book form. The current volume is *Medical Progress: Annual, 1940* (Springfield, Illinois: Charles C Thomas Company, 1941. \$4.00).

\*This article comprises a seminar held by the Department of Pharmacology, Yale University School of Medicine, on January 26, 1942. Among the various members contributing, I am especially indebted to my colleague, Professor George R. Cowgill, and to my associate, Dr. Rigby C. Roskelley.

The first part was presented in the April 16 issue of the *Journal*.

†Professor of pharmacology, Yale University School of Medicine.

used, as suggested by von Euler.<sup>70</sup> The determination of coenzyme I can be made simply in the Warburg micromanometric device under carefully controlled conditions. The basis of the method is that, when varying amounts of coenzyme are added to a washed preparation of yeast, the ensuing rate of fermentation is proportional, within certain limits, to the coenzyme I concentration. The measurement involves the rate of evolution of carbon dioxide resulting when the following mixture is allowed to interact: washed yeast, glucose magnesium or manganese ion and hexosediphosphate, properly buffered at the optimal pH.

This method may be applied to extracts prepared from tissue and from the red cells of the blood. Thus, von Euler and Malmberg<sup>71</sup> found that human red cells contained 20 to 35 microgm. of coenzyme I per gram of fresh red cells. Even higher values were found by Elvehjem et al.<sup>69</sup> for the red cells of dogs deficient in nicotinic acid, namely, 60 to 66 microgm. per gram of fresh tissue which is the same as that found in normal dogs. However, Elvehjem and his associates observed that in man the normal value of 20 to 30 microgm. per cubic centimeter of blood might increase to 60 microgm. after the injection of 100 mg. of nicotinic acid a day. This was true of both normal patients and those with pellagra. When this high level had been reached after several days of such therapy, and when the nicotinic acid medication was stopped, the cozymase content of the blood gradually decreased to the normal level in the course of a fortnight. These results confirmed similar results of Kohn.<sup>72</sup> Like blood thiamin, the nicotinic acid seems to be converted into cozymase only in the corpuscles. In other words, it is chiefly the erythrocytes that contribute the enzymic activity of the whole blood.

It is evident, therefore, that the study of the blood is not of great diagnostic help because that of normal and deficient animals does not differ significantly. Thus, Axelrod, Spies and Elvehjem<sup>73</sup> found an average value of 85 microgm. per cubic centimeter of erythrocytes for normal people, as against 69 microgm. in patients with mild pellagra. Similarly, in 5 cases of severe pellagra, values ranged between 70 and 90 microgm. per cubic

centimeter of erythrocytes. It is true, as found by Axelrod, Madden and Elvehjem,<sup>74</sup> that the liver and muscle tissues from deficient animals contain considerably less cozymase than the same tissues from normal animals. In 9 normal subjects, the value per gram of fresh muscle was 382 microgm. of coenzyme I, as against 214 microgm. in 5 patients with severe pellagra. This procedure, however, is not a very practical one under clinical conditions. When nicotinic acid is administered to patients with pellagra, a marked increase in the coenzyme I contents of both the red cells and the muscle occurs, as found by Axelrod, Gordon and Elvehjem and their collaborators.

Vilter et al.<sup>75,76</sup> showed that marked decreases in coenzyme I or II may occur in severe diabetic acidosis or in leukemia, and perhaps also in roentgen-ray sickness and pneumococcal pneumonia. Evidence is presented that the corpuscles merely store the vitamin, rather than actually synthesizing it.<sup>77</sup> These authors, in fact, have found low values in several severe clinical syndromes, as have Justin-Besançon and his associates.<sup>78</sup>

After the intravenous administration of nicotinic acid, the major part of the free vitamin disappears from the blood in half an hour, according to von Euler and Schlenk.<sup>79</sup> Not over one eighth of the total blood vitamin is in the free form normally. Indeed, Kodicek<sup>80</sup> believes that there may be no free vitamin normally. After hydrolysis, the whole blood yields between 1 and 5 microgm. per cubic centimeter. Kühnau<sup>81</sup> found 2.5 to 4.5 microgm per cubic centimeter of whole blood, and Patton, Sutton and Youmans<sup>82</sup> 3 to 5 microgm. Although vitamin-deficient patients tended to have somewhat lower values than normal, this finding was not strikingly consistent. Kohn,<sup>83</sup> who suggested that coenzyme should be expressed per volume of corpuscles, observed the equivalent of 10 to 18 microgm. of combined nicotinic acid per cubic centimeter of human corpuscles (or 50 to 90 microgm. of enzyme).

In summary, it is necessary in determinations of cozymase and nicotinic acid, as in those of the two varieties of vitamin B already considered, to have recourse to urinary studies and particularly to vitamin-tolerance tests.

#### *Nicotinic Acid in Urine*

Methods are now available for determining colorimetrically the urinary excretion of nicotinic acid, nicotinamide and nicotinuric acid, together with other possible derivatives closely related to these substances. Under ordinary circumstances, it is found, as reported by Rosenblum and Jolliffe,<sup>84</sup> that in twenty-four hours approximately 3 to 10 mg. of these substances is excreted by normal per-

sons. Perlzweig, Levy and Sarett<sup>85</sup> observed that in 5 normal human adults on an adequate diet, the average daily excretion of nicotinic acid derivatives (exclusive of trigonelline) was 1 to 3 mg. Furthermore, daily trigonelline excretion on a diet free of coffee was 20 to 29 mg. but approximately 200 mg. when the diet included coffee. As pointed out below, nicotine excretion by tobacco smokers may complicate the analysis if special precautions are not taken.

In the twenty-four-hour urine of well-nourished subjects, Melnick, Robinson and Field<sup>86</sup> found from 1.7 to 29.3 mg. and Patton, Sutton and Youmans<sup>82</sup> 3 to 5 mg. In the urine of patients with advanced pellagra, Vilter, Spies and Mathews<sup>87</sup> were unable to find nicotinic acid. In less advanced cases, Kühnau<sup>81</sup> found urinary concentrations in the lower range of normal, that is, 64 to 105 microgm. per 100 cc.

Rosenblum and Jolliffe<sup>84</sup> also noted that, in a patient with pellagra, urinary nicotinic acid was very low and ultimately disappeared as the patient continued on a diet low in vitamin B complex. When such a patient was put on a diet high in vitamin B complex, however, the urinary nicotinic acid excretion rose within a day to normal levels, and subsequently on a daily intake of 100 mg. of nicotinic acid, excretion reached a peak of approximately 10 mg. in twenty-four hours. Indeed, Perlzweig, Levy and Sarett<sup>85</sup> found that after the ingestion of doses of nicotinic acid as high as 100 to 200 mg., normal adults might excrete 3 to 19 mg. of nicotinic acid derivatives, mostly in the form of nicotinuric acid. This represented a recovery of from 10 to 25 per cent. At the same time, there was a definite change in trigonelline excretion.

Several other investigators have studied the retention of excessive doses of the vitamin in normal subjects and in patients with pellagra. In normal controls, the postprandial administration of 500 mg. of nicotinic acid led to a rapid increase in urinary excretion, according to Melnick, Robinson and Field.<sup>86</sup> This amounted to 22 per cent of the test dose, and was excreted mainly in the form of trigonelline and nicotinic acid. Even with a small dose of 50 mg., Najjar and Wood<sup>88</sup> found that the urinary concentration increased approximately tenfold within four hours. Using oral doses of from 150 to 300 mg. of nicotinic acid or its amide, Patton, Sutton and Youmans<sup>82</sup> were able to recover about 20 per cent of the dose within three hours; after this time, however, no extra vitamin appeared in the urine. Parallel observations on deficient subjects yielded only 3 per cent. With a test dose of 100 mg. of nicotinic acid, Swaminathan<sup>89</sup> obtained the following in-



structive results, expressed as twenty-four-hour excretions:

SUBJECT	NORMAL EXCRE- TION	EXCRETION AFTER TEST DOSE
	mg.	mg.
Well-nourished wheat eaters .	6.8	27.9
Well-nourished rice eaters .	3.2	19.7
Poorly nourished persons	1.3	9.8
Deficiency patients	1.2	5.1

Therefore, the concentration of the vitamin and its derivatives found in the urine is of considerable help in confirming the diagnosis of vitamin deficiency. At present, few determinations are available to indicate whether the so-called "tolerance curve" can be used as a determination of the extent of saturation or unsaturation of the tissues at large. The evidence to date, however, suggests that the vitamin-tolerance curves in these cases, as in those of thiamin deficiency, may be used to measure avidity of the tissues for nicotinic acid.

Several colorimetric methods have been applied to the determination of the nicotinic acid in urine. Most of these are based on color reactions produced by the pyridine ring. Thus, Vilter, Spies and Mathews<sup>87</sup> and Karrer and Keller<sup>90</sup> employed 2,4-dinitrochlorobenzene in the presence of an alkali hydroxide. Similarly, Shaw and MacDonald<sup>91</sup> and Patton, Sutton and Youmans<sup>82</sup> used the reaction with cyanogen bromide in the presence of aniline. Melnick and Field<sup>92</sup> studied the limitations of this method carefully. Ritsert<sup>93</sup> and Pearson<sup>94</sup> and Harris and Raymond<sup>95</sup> have also applied this reaction, the last named using *p*-aminoacetophenone.

More satisfactory is the colorimetric procedure of Bandier and Hald.<sup>96</sup> In their modification, *p*-methylaminophenol sulfate (Metol-Agfa) was allowed to react with nicotinic acid and cyanogen bromide in aqueous solution in the presence of potassium acid phosphate. Under these circumstances, a clear yellow color was obtained that was constant, stable and directly proportional to the concentration of nicotinic acid or of nicotinamide. Several other pyridine derivatives, including trigonelline, failed to give any color. This method has been further modified by Rosenblum and Jolliffe,<sup>84</sup> and by Perlzweig, Levy and Sarett.<sup>85</sup> The method is convenient and is suitable for most clinical research. The final solution may be analyzed chemically with an electrophotometer. Even in urine from heavy users of tobacco or from coffee habitués, this method has given satisfactory results.

Some investigators have used the so-called "V-factor" as a measure of nicotinic acid deficiency. This factor comprises the combined effects of

coenzymes I and II and possibly some other unknown related substances. It is frequently measured by a microbiologic test involving the growth of influenza bacilli. Dorfman, Horwitt and Koser<sup>81</sup> applied this method to human blood and urine, and obtained very consistent results. Likewise, Kohn, Bernheim and Felsony<sup>98</sup> have used the procedure in normal and pathologic subjects, including patients with diabetes, pulmonary disease and pellagra. They found a considerable overlapping of the pathologic and normal patients regarding the content of this factor in corpuscles. Consequently, this method is less desirable for most purposes than the chemical tests mentioned above.

The problem of nicotinic acid metabolism is still complicated by a lack of understanding of the metabolic significance of trigonelline, the betaine of nicotinic acid, and other pyridine derivatives that appear in the urine. Some of these may perhaps be derived from foodstuffs, especially those from seedlike sources. The possibilities are so complex as to make the interpretation of urinary data often difficult. Perlzweig and his associates,<sup>85</sup> moreover, have pointed out that there are considerable differences among several species of animals, and therefore one cannot lean too heavily on collateral animal studies in evaluating observations on man.

#### VITAMIN C (ASCORBIC ACID)

A great deal of work has been done with the physiology of ascorbic acid, otherwise known as cevitamic acid. Consequently, it is possible to mention only a few selected investigations with which I am familiar. For clinical work, the classic methods of bioassay are not practical because they involve the use of many animals. Such methods on rare occasions may be used to check the specificity of chemical methods. For example, occasionally it may be found in the analysis of certain vegetables that a false titer is given by chemical methods as judged by the effect on the scorbutic guinea-pig tooth. Under ordinary circumstances, however, chemical methods are quite adequate for clinical study.

#### Methods

The chief chemical procedures used at present employ modifications of Tillmans's<sup>99</sup> original reagent, the value of which depends on the color loss of an oxidation-reduction indicator known chemically as 2, 6, dichlorophenolindophenol. The use of this indicator has been justified by many observations, such as those of Bessey and King.<sup>100</sup> In this method, under standard conditions, the colored titration solution is rapidly reduced in acid

olution to a colorless compound. The reagent thus serves as its own indicator. Ordinarily, metaphosphoric acid is used as an acid-extractant because it has marked protective properties and is inert toward the indicator.

The basis of this reaction, of course, is the striking reducing effect of the double bond that occurs in the molecule of ascorbic acid between the second and third carbon atoms. Accordingly, the test records only the reduced form of ascorbic acid. Indeed, certain discrepancies have arisen because the oxidized form, which is unstable, is not estimated by this procedure. Some of the complications caused by the presence of other reducing substances have been discussed by Bessey.<sup>101</sup>

In general, it may be said that these difficulties have been largely circumvented in assays of blood and urine. The method for blood is well represented by the procedure of Abt, Farmer and Epstein.<sup>102</sup> In brief, plasma from oxalated blood is treated with metaphosphoric acid to remove protein, and the protein-free fluid is titrated with a standard solution of Tillmans's reagent. This procedure requires 2 cc. of plasma. The final titration is made with a 5-cc. microburette. A stock solution of the dye is made up containing 0.2 gm. per 100 cc. For daily use, it is diluted tenfold and is standardized against small amounts of ascorbic acid.

Various convenient modifications of this method have been made, but Bessey<sup>101</sup> has adapted the technique to photoelectric colorimetry. Furthermore, Findlin and Butler<sup>103</sup> have developed a micro-method that is satisfactory for children and requires only 0.2 cc. of capillary blood. Characteristic values obtained in the clinic may be found in the article by Pijouan and Klemperer.<sup>104</sup>

The determination of ascorbic acid in urine by the use of Tillmans's reagent has been described by many investigators. Convenient methods are those of Harris and his collaborators<sup>105</sup> for the titrimetric procedure and of Evelyn, Malloy and Rosen<sup>106</sup> for the photometric procedure.

Of special interest is the determination of vitamin C in the leukocytes of the blood as described by Stephens and Hawley<sup>107</sup> and more recently by Brandon, Lund and Dill.<sup>108</sup>

#### Blood Content

As stated above, blood analysis is of little clinical value in the determination of the vitamin B complex. The blood ascorbic acid, on the contrary, can yield definite information, although such information must be interpreted in the light of repeated tests. There is a distinct relation between the level of ascorbic acid in the blood plasma and the dietary intake, as shown by many observers. This problem has been studied carefully

by Thyssell.<sup>109</sup> The problem has been studied further by Farmer,<sup>110</sup> who points out that, in general, certain levels may be assigned to characteristic dietary intakes. Thus, if the diet contains less than 15 mg. a day, the blood ascorbic acid level may be expected to be less than 0.2 mg. per 100 cc.; under 30 mg. a day, less than 0.4 mg. per 100 cc.; under 50 mg. a day, less than 0.6 mg. per 100 cc.; under 100 mg. a day, ranging between 0.4 and 0.8 mg. per 100 cc. If the dietary intake is more than 100 mg. of ascorbic acid daily, the blood ascorbic acid may be expected to fall between 1.0 and 2.0 mg. per 100 cc. Wolff, Banning and van Eekelen<sup>111</sup> believe that for optimal nutrition the blood plasma should contain more than 1.2 mg. per 100 cc.

Thus, although some indication may be had of the general range of vitamin nutrition from the level in the blood, it must be emphasized that this is true only when repeated determinations are made or when groups of individual studies are compared. Butler<sup>112</sup> has pointed out that even in persons who are not in dire danger of scurvy the plasma level may fall to nil at times, although the tissues are tolerably well saturated with the vitamin. In other words, the blood is a carrier system for the vitamin, but the equilibrium is not necessarily reversible, so that the blood level may fall even though the tissues still contain considerable stores of ascorbic acid. Thus, in a study of human experimental scurvy, Lund and Crandon<sup>113</sup> found that on a scurvy-producing diet the ascorbic acid level of the blood plasma fell to zero in forty-two days, and that of the white cells in the blood in one hundred and twenty-two days. Nevertheless, the first definite signs of scurvy did not appear for five months, and the symptoms were not severe for six months. Therefore, several investigators in this field do not agree with the conclusions of van Eekelen, Emmerie and Wolff<sup>114</sup> that the degree of vitamin C saturation can be estimated by a single blood determination.

It is true that, in general, there is a straight-line relation between the initial ascorbic acid content of the blood and the total quantity of vitamin needed to saturate the subject. Nevertheless, most investigators prefer to study urinary excretions under standard conditions to determine the need of the patient's tissues for the vitamin. This problem has been discussed by Portnoy and Wilkinson.<sup>115</sup> One source of trouble is the fact, emphasized by Heinemann,<sup>116</sup> that there is a sort of renal threshold for ascorbic acid. Indeed, urinary excretion is relatively slight until the serum level reaches approximately 1.3 to 1.4 mg. per 100 cc., whereupon a sharp rise in urinary out-

put occurs. Moreover, this threshold seems to be influenced by several factors.

### *Urinary Excretion*

It was recognized several years ago that in the presence of ascorbic acid deficiency the daily urinary excretion is low. The chief point of discussion has been the quantitative one of how low the excretion may go without indicating that frank vitamin deficiency is present. Originally, Harris and his associates<sup>117</sup> concluded that if a subject excretes less than 13 mg. of ascorbic acid a day he is probably suffering from vitamin deficiency. For a subject to be optimally saturated with the vitamin, van Eekelen and Heinemann<sup>118</sup> believe that a daily excretion of 40 mg. should be maintained.

Many investigators maintain that a much surer way of testing subjects is to study their retention after a test dose of the vitamin. Various procedures have been used involving different doses. The most frequent is that of administering 5 mg. per pound of body weight as recommended by Harris and his co-workers.<sup>117</sup> The vitamin is ordinarily given by mouth, and within the following twenty-four hours it is expected that a saturated subject will excrete more than half the entire dose. For larger doses, less is recovered, and for smaller doses somewhat more on a percentage basis. Indeed, van Eekelen and Heinemann found that when 300 mg. was given subcutaneously to a saturated patient it was entirely excreted within six hours.

A convenient combination of blood and urine tests has been developed by Kastlin et al.<sup>119</sup> This method involves the intravenous administration of 500 mg. of ascorbic acid and the observation of the blood and urine responses for four hours. The results of blood and urine are plotted in the form of curves. Thus, in a normal person, the blood level rises from the fasting level of about 0.7 mg. to about 7 mg. per 100 cc., and then falls very gradually. During the same time, in the course of four hours, the urinary excretion should be over 40 per cent of the test dose. By contrast, if a deficiency exists, only a slight rise in the blood level above the fasting level occurs, and this rise is variable and is rapidly lost as the tissues take up the vitamin. Simultaneously, the urinary excretion is less than 20 per cent of the test dose in the course of the four-hour period. These curves are, in essence, vitamin-tolerance curves, both for blood and urine. The simultaneous use of these two body fluids increases considerably the reliability of the results.

### *Saturation Tests*

More complicated procedures have been employed in investigations involving the administra-

tion of the vitamin over the course of several days. Gander and Niederberger<sup>120</sup> determined the total quantity of ascorbic acid needed before saturation was reached. This figure is sometimes known as the "saturation deficit." Similarly, standard test doses have been given daily for a number of days until saturation is reached; the number of days required under these conditions has been used as an index of the vitamin C deficiency. Such a method was employed by Jezler and Kapp.<sup>121</sup> In general, however, such methods are too time-consuming to be practicable except in scientific or fundamental clinical investigations.

### *Clinical Applications*

Of course, such tests have additional usefulness in the detection of latent scurvy. Nevertheless, it has become clear as the result of frequent studies by numerous investigators that the dietary is not the only variable involved. Faulkner and Taylor<sup>122</sup> found that in patients with rheumatic and other infections the vitamin C requirement is high and that such patients often lack optimal stores of the vitamin. Pregnancy and lactation also increase the demand for the vitamin. Some of these factors have been reviewed by Robertson<sup>123</sup> and by Perla and Marmorston.<sup>124</sup> Keith and Hickmans<sup>125</sup> have also found marked deficiency of vitamin C in children with rheumatic fever or chronic rheumatism.

In 1927, Aron<sup>126</sup> reported that in scorbutic children cutaneous wounds often failed to heal whereas following vitamin C therapy they healed quickly. Since then, there has been increased interest on the part of surgeons in this problem. Lanman and Ingalls<sup>127</sup> report the case of a six-week-old infant with spontaneous opening of a laparotomy wound in the presence of scurvy. Similar results were obtained by Taffel and Harvey.<sup>128</sup> This problem has recently been studied in man by Lund and Crandon.<sup>113</sup> These investigators concluded that lack of vitamin C is a possible factor in failure of wound healing, particularly in patients with a long and continued avitaminosis. Their observations cast some doubt on the role of ascorbic acid in the production of anemia, however.

### EXTENT OF VITAMIN DEFICIENCY

There is at present considerable disagreement about the extent of malnutrition in the United States. On the one side of the question, one finds the clinical experience of Alvarez<sup>129</sup> and others that gross disease due to avitaminosis is not often recognized in highly reputable clinics. In his inimitable manner, Clendening<sup>130</sup> has presented this side of the case, addressed particularly to readers who have a sense of humor. On the other side, one finds the estimate by Parran<sup>131</sup> that 45,000,000

people in this country do not enjoy optimal vitamin nutrition. This figure is based on the careful study of four thousand American dietaries by Suebeling and Phipard<sup>132</sup>

The problem boils down to what has been called "hidden hunger," which, by definition, can not be diagnosed clinically. How important this state may be in the daily lives of the apparently healthy or of the obviously ill can be answered only when careful functional studies, physiologic and psychologic, are correlated with carefully measured vitamin metabolism. Such a study, indeed, is now in progress at the Lockheed Aviation Plant in Los Angeles as part of a program recommended by the Committee on Nutrition in Industry of the National Research Council.

In the meantime, chemical studies can be applied in the routine clinic to ascertain how great a factor of safety has been afforded by the diet in the individual case. Until it is clear how low a saturation can be tolerated, obviously the safest policy is to ensure liberal replenishment of vitamin stores. In chronic illnesses accompanied by restriction of food, whether spontaneous or enforced, mild vitamin deficiency may lurk unsuspected in the background as a contributory element in the total discomfiture of the patient.

Such data must, of course, be correlated with parallel clinical observations. For example, examination with the slit lamp<sup>133</sup> may be utilized to detect characteristic changes in the corneas of patients deficient in vitamin B<sub>2</sub>, or to detect Bitot spots<sup>134, 135</sup> due to lack of vitamin A. Likewise, the study of other chemical substances, such as pyruvic acid metabolism in vitamin B<sub>1</sub> deficiency, may give specific evidence of disturbed nutrition.<sup>136</sup> At the present time, there is need of many such collateral data before final conclusions can be drawn. Eventually, however, chemical data will afford a convenient parameter by which to integrate many facts drawn from diverse sources.<sup>137</sup> Indeed, Mason and Williams<sup>138</sup> have recently emphasized the utility of such a procedure in clinical studies of thiamin deficiency. This will be particularly valuable in cases of conditioned deficiency, when the nature of the dietary offers little clue to the nutritional status of the patient.

\* \* \*

It may be recalled that convenient methods are available for determining the concentration of the commonly known vitamins in the blood and excreta of human subjects. The use of these procedures has been extended to various types of tolerance and saturation tests. These serve to estimate the extent of tissue stores of vitamin and the avidity with which body tissues retain vitamin. In general, studies of urinary excretion are probably

more significant than the analysis of blood, except in investigations of vitamin A.

The interpretation of the results obtained by these tests requires further statistical study. How impoverished in vitamin must a patient be before he is considered unhealthy? Obviously, a biochemical method cannot answer this question, but it can at least measure the degree of vitamin lack. Already, there is considerable evidence that in Minot's "twilight zone" of subclinical vitamin lack, human efficiency and effectiveness may be greatly impaired. In the impending strain on national resources, this approach will assume particular importance.

333 Cedar Street

# REFERENCES

- 65 Warburg O and Christian W Co-Fermentproblem *Biochem Ztschr* 275 464 1935
- 66 Elvehjem C A Madden R J Strong F M and Woolley D W The isolation and identification of the anti black tongue factor *J Biol Chem* 123 137 149 1938
- 67 Spies T D Bean W B and Ashe W F Recent advances in the treatment of pellagra and associated deficiencies *Ann Int Med* 17 1830 1844 1929
- 68 Mueller J H Nicotinic acid as growth accessory for diphtheria bacillus *J Biol Chem* 120 219 224 1937
- 69 Axelrod A E Gordon L S and Elvehjem C A The relation of the dietary intake of nicotinic acid to the coenzyme I content of blood *Am J M Sc* 199 697 705 1940
- 70 von Euler H Die Cozymase *Ergebn d Physiol* 38 130 1936
- 71 von Euler H and Malmberg M Aktivatoren des Kohlenhydratstoffwechsels als wasserlösliche Nahrungskomponenten *Biochem Ztschr* 284 405 469 1936
- 72 Kohn H I Concentration of coenzyme I like substances in the blood following the administration of nicotinic acid to normal and vitamin deficient rats *Biochem J* 32 20 5-2083 1938
- 73 Axelrod A E Spies T D and Elvehjem C A The effect of a nicotinic acid deficiency upon the coenzyme I content of the human erythrocyte and muscle *J Biol Chem* 138 667 676 1941
- 74 Axelrod A E Madden R J and Elvehjem C A The effect of a nicotinic acid deficiency upon the coenzyme I content of animal tissues *J Biol Chem* 151 85 93 1939
- 75 Vilter R W Vilter S P and Spies T D Synthesis of coenzymes I and II *Nature* 144 943 1939
- 76 Vilter S P Hoch M B and Spies T D Coenzymes I and II in human blood *J Lab & Clin Med* 26 31-44 1940
- 77 Vilter R W Vilter S P and Spies T D Determination of the coenzyme I and II (cozymase) in the blood of diabetic and normal subjects *Am J M Sc* 197 322 326 1939
- 78 Justin Besancon L Lwoff A Querdo A Imbony J M Etudes sur le taux de l'amide nicotique dans le sang à l'état pathologique *Bull ex mem Soc med d hop de Paris* 55 1217 1224 1939
- 79 von Euler H and Schlenk F Nicotinsäure und Cozymase im Blut *Klin Wchnschr* 18 1109 1111 1939
- 80 Kordick E Estimation of nicotinic acid in animal tissues, blood and certain foodstuffs. II Application *Biochem J* 34 724 735 1940
- 81 Kubnu W W Ueber das Verhalten der Nicotinsäure in den Körper saften bei Pellagra und bei Gesunden *Klin Wchnschr* 18 1333 1939
- 82 Pitton E W Sutton W R and Youmans J B Studies on the nicotinic acid content of blood and urine *J Clin Investigation* 19 785 1940
- 83 Kohn H The determination of V factor (coenzyme) in blood *Am J Physiol* 129 1398 1940
- 84 Rosenblum L A and Joffe N Application to urine of Band er and Hild's method for determination of nicotinic acid *J Biol Chem* 134 137 141 1940
- 85 Perlzweig W A Levy E D and Sarett H P Nicotinic acid derivatives in human urine and their determination *J Biol Chem* 136 229 45 1940
- 86 Melnick D Robinson W D and Field H Jr Urinary excretion of nicotinic acid and its derivatives by normal and vitamin deficient rats *J Biol Chem* 136 145 156 1940
- 87 Vilter S P Spies T D and Mathews A P A method for the determination of nicotinic acid, nicotinamide, and possibly other pyridine like substances in human urine *J Biol Chem* 125 95 93 1938
- 88 Najjar V A and Wood R W Presence of a hitherto unrecognized nicotinic acid derivative in human urine *Proc Soc Exper Biol Med* 44 386 390 1940
- 89 Swann nathan M Urinary excretion of nicotinic acid *Ind an J M Research* 27 417 428 1939
- 90 Karper P and Keller H Eine kolorimetrische Bestimmung des Nicotinsäureamids *Helvet chim acta* 21 463-469 1938
- 91 Shaw G E and MacDonald C A A colorimetric estimation of nicotinic acid as applied to commercial and liver extracts *Quart J Pharm & Pharmacol* 11 330-339 1938
- 92 Melnick D and Field H Jr Determination of nicotinic acid in biological materials by means of photometric colorimetry *J Biol Chem* 134 116 1940

93. Ritsert, K. Zur quantitativen Nicotinsäure- und Nicotinsäure-amid-Bestimmung im Harn, in Geweben und im Blut. *Klin. Wchnschr.* 18:934-936, 1939.
94. Pearson, P. B. The nicotinic acid content of the blood of mammalia. *J. Biol. Chem.* 129:491-494, 1939.
95. Harris, L. J., and Raymond, W. D. Assessment of the level of nutrition. A method for the estimation of nicotinic acid in urine. *Biochem. J.* 33:2037-2051, 1939.
96. Bandier, E., and Hald, J. A colorimetric reaction for the quantitative estimation of nicotinic acid. *Biochem. J.* 33:264-271, 1939.
- Bandier, E. Quantitative estimation of nicotinic acid in biological material. *Ibid.* 33:1130-1134, 1939.
97. Dorfman, A., Horvitt, M. K., Koser, S. A., and Saunders, F. The use of the dysentery organism for the quantitative determination of nicotinic acid. *J. Biol. Chem.: Sci. Proc.* 128:xx, 1939.
98. Kohn, H. I., Bernheim, F., and Felsovanyi, A. V. The blood V-factor (coenzyme) level in normal and pathological subjects. *J. Clin. Investigation* 18:585-591, 1939.
99. Tillmans, J., Hirsch, P., and Hirsch, W. Das Reduktionsvermögen pflanzlicher Lebensmittel und seine Beziehung zum Vitamin C. I. Der reduzierende Stoff des Citronensaftes. *Ztschr. f. Untersuch. d. Lebensmitt.* 63:1-21, 1932.
100. Bessey, O. A., and King, C. G. The distribution of vitamin C in plant and animal tissues, and its determination. *J. Biol. Chem.* 103:687-698, 1933.
101. Bessey, O. A. A method for the determination of small quantities of ascorbic acid and dehydroascorbic acid in turbid and colored solutions in the presence of other reducing substances. *J. Biol. Chem.* 126:771-784, 1938.
102. Abt, A. F., Farmer, C. J., and Epstein, I. M. Normal ascorbic (ascorbic) acid determinations in blood plasma and their relationship to capillary resistance. *J. Pediat.* 8:1-19, 1936.
103. Mindlin, R. L., and Butler, A. M. The determination of ascorbic acid in plasma: a macromethod and a micromethod. *J. Biol. Chem.* 122:673-686, 1938.
104. Pijoan, M., and Klemperer, F. Determination of blood ascorbic acid. *J. Clin. Investigation* 16:443-445, 1937.
105. Abbasy, M. A., Harris, L. J., Ray, S. N., and Marrack, J. R. Diagnosis of vitamin-C subnutrition by urine analysis: quantitative data-experiments on control subjects. *Lancet* 2:1399-1405, 1935.
106. Evelyn, K. A., Malloy, H. T., and Rosen, C. The determination of ascorbic acid in urine with the photoelectric colorimeter. *J. Biol. Chem.* 126:645-654, 1938.
107. Stephens, D. J., and Hawley, E. E. Partition of reduced ascorbic acid in blood. *J. Biol. Chem.* 115:653-658, 1936.
108. Crandon, J. H., Lund, C. C., and Dill, D. B. Experimental human scurvy. *New Eng. J. Med.* 223:353-369, 1940.
109. Thysell, T. C-Vitaminstandard und C-Hypovitaminose; über Kost, Blutascorbinsäure und Kapillarblutungsprobe. *Acta paediat.* 26:481-488, 1939.
110. Farmer, C. J. Vitamin C analysis in relation to clinical problems. *Quart. Bull. Northwestern Univ. Med. School* 14:220-235, 1940.
111. Wolff, L. K., Banning, C., and van Eckelen, M. Nutrition of various groups of families in the Netherlands showing vitamin A and C content, and investigation of blood and urine for presence of these two vitamins. *Quart. Bull. Health Organ., League of Nations* 5:566-570, 1936.
112. Butler, A. M. Personal communication.
113. Lund, C. C., and Crandon, J. H. Human experimental scurvy and the relation of vitamin C deficiency to postoperative pneumonia and to wound healing. *J. A. M. A.* 116:663-668, 1941.
114. van Eckelen, M., Emmeric, A., and Wolff, L. K. Über die Diagnostik der Hypovitaminosen A und C durch die Bestimmung dieser Vitamine im Blut. *Ztschr. f. Vitaminforsch.* 6:150-162, 1937.
115. Portnoy, B., and Wilkinson, J. F. Vitamin C deficiency in rabbit ulceration and hematemesis. *Brit. M. J.* 1:554-560, 1938.
116. Heinemann, M. On the relation between diet and urinary excretion of thiosulphate and ascorbic acid. II. Human requirements for vitamin C. *Biochem. J.* 30:2299-2306, 1936.
117. Harris, L. J., Abbasy, M. A., Yudkin, J., and Kelly, S. Vitamin in human nutrition: vitamin-C reserves of subjects of a voluntary hospital class. *Lancet* 1:1488-1490, 1936.
118. van Eckelen, M., and Heinemann, M. Critical remarks on the determination of urinary excretion of ascorbic acid. *J. Clin. Investigation* 17:293-299, 1938.
119. Kastlin, G. J., King, C. G., Schlesinger, C. R., and Mitchell, J. W. Chemical methods for the determination of clinical vitamin C (ascorbic acid) deficiency. *Am. J. Clin. Path.* 10:882-893, 1940.
120. Gander, J., and Niederberger, W. Über den Vitamin C-Bedarf alter Leute. *München. med. Wchnschr.* 83:1386-1389, 1936.
121. Jezler, A., and Kapp, H. Zur Frage des Vitamin C-Defizits. *Ztschr. f. klin. Med.* 130:178-192, 1936.
122. Faulkner, J. M., and Taylor, F. H. L. Observations on renal threshold for ascorbic acid in man. *J. Clin. Investigation* 17:69-75, 1938.
123. Robertson, E. C. The vitamins and resistance to infection. *Medicine* 13:123-206, 1934.
124. Perla, D., and Marmorston, J. The role of vitamin C in resistance. *Arch. Path.* 23:543-575, 683-712, 1937.
125. Keith, J. D., and Hickmans, E. M. Vitamin C excretion in children, with particular reference to rheumatic fever. *Arch. Dis. Child.* 13:125-136, 1938.
126. Aron, H. *Die Nährschäden des Kindes, ihre Entstehung, Verhütung und Heilung. Ein Leitfaden für die Praxis.* 152 pp. Berlin: Urban & Schwarzenberg, 1927. P. 103.
127. Lanman, T. H., and Ingalls, T. H. Vitamin C deficiency and wound healing: experimental and clinical study. *Ann. Surg.* 105:616-625, 1937.
128. Taffel, M., and Harvey, S. C. The effect of absolute and partial vitamin C deficiency on healing of wounds. *Proc. Soc. Exper. Biol. & Med.* 38:518-525, 1938.
129. Alvarez, W. C. Cited by Clendening.<sup>130</sup>
130. Clendening, L. The national nutrition. *J. A. M. A.* 117:1935, 1941.
131. Parran, T. Nutrition and national health. Dietary deficiency is widespread and serious with more than 40% of the population on inadequate rations: nutritional defects as sources of disease. *Technology Rev.* 42:323-348, 1940.
132. Stiebeling, H. K., and Shipard, E. F. *Diets of Families of Employed Wage Earners and Clerical Workers in Cities.* United States Department of Agriculture Circular No. 507. 141 pp. Washington: Government Printing Office, 1939.
133. Sydenstricker, V. P., Sebrell, W. H., Cleckley, H. M., and Kruse, H. D. The ocular manifestations of ariboflavinosis: a progress note. *J. A. M. A.* 114:2437-2445, 1940.
134. Kruse, H. D. Medical evaluation of nutritional states. IV. The ocular manifestations of avitaminosis A with especial consideration of the detection of early changes by biomicroscopy. *Pub. Health Rep.* 50:1301-1324, 1941.
135. Wiedl, D. G., and Kruse, H. D. V. The prevalence of deficiency diseases in their subclinical stages. *Milbank Mem. Fund Quart.* 19:241-251, 1941.
136. Platt, B. S., and Lu, G. D. Studies on the metabolism of pyruvic acid in normal and vitamin B<sub>1</sub>-deficient states. IV. The accumulation of pyruvic acid and other carbonyl compounds in beri-beri and the effect of vitamin B<sub>1</sub>. *Biochem. J.* 33:1525-1537, 1939.
137. Subcommittee on Medical Nutrition, Division of Medical Sciences, National Research Council. Recognition of early nutritional failure in infants, children, adolescents and adults. *J. A. M. A.* 118:645, 1942.
138. Mason, H. L., and Williams, R. D. The urinary excretion of thiamine as an index of the nutritional level: assessment of the value of a test dose. *J. Clin. Investigation* 21:247-255, 1942.

# CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTE-MORTEM AND POST-MORTEM RECORDS AS USED  
IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

## CASE 28171

### PRESENTATION OF CASE

A seventy-year-old Irish-American was admitted to the hospital because of tarry stools.

About thirteen months before entry, the patient noticed that his stools frequently included small amounts of bright-red blood or streaks of dark blood, or occasionally were frankly tarry. Bowel movements continued regular, without resort to cathartics. There was no pain or distention. The patient visited the clinic of another hospital and had a roentgenologic examination of the gastrointestinal tract that was said to be negative; the symptoms continued, as before. A week before entry, he consulted the clinic of this hospital and was proctoscoped, with visualization of small, high internal hemorrhoids. A roentgenogram of the colon showed an irregular narrowing of the lumen of the midsigmoid, over a distance of 6 cm. The proximal end showed a "slightly intussuscepting" filling defect. The mucosal pattern in this area was abnormal. There were several diverticula of the sigmoid and lower descending colon. The remainder of the colon, the appendix and the terminal ileum appeared normal.

Two sisters of the patient had died of tuberculosis. When he was between twenty and thirty years old, the patient had several "nervous breakdowns" characterized by personality disturbances and dipsomania. For many years after this, he experienced occasional nausea and vomiting after breakfast. Five years before entry, he had hemorrhoids removed at another hospital. Three years later, after a period of urinary frequency terminating in an episode of acute retention, the patient had a two-stage prostatectomy, also in the other hospital. At about this time, he developed an eruption on the left cheek. A year later, he consulted the clinic of this hospital. Biopsy of the lesion, three months before entry, showed carcinoma of undetermined type. In the following month, 4300 r of roentgen therapy was given to the cheek, with resultant regression of the lesion.

On admission, the patient appeared well preserved, plethoric and in good health. A mottled scar, 2 cm. in diameter, lay on the left midcheek. The heart and lungs were essentially normal. The abdomen was soft, with an elongated mass

in the left lower quadrant that could be rolled between the examiner's fingers. There were no other palpable masses. There was a small hernia at the site of a midline suprapubic old operative incision, and a right direct inguinal hernia. Rectal examination was negative.

The blood pressure was 240 systolic, 120 diastolic. The pulse, temperature and respirations were normal.

Examination of the blood showed a red-cell count of 4,900,000 with 90 per cent hemoglobin, and a white-cell count of 7800 with 66 per cent polymorphonuclears. The urine was normal.

A roentgenogram of the chest showed only tortuosity of the aorta, and old calcified tuberculous foci in both upper lobes. An electrocardiogram showed changes consistent with either hypertensive or coronary heart disease.

On the third hospital day, cecostomy and appendectomy were performed under local anesthesia. There was little postoperative reaction, and the cecostomy tube drained well. A roentgenogram of the large bowel showed marked delay in passage of barium above the abnormal area noted in the previous examination.

On the fourteenth hospital day, a second operation was performed.

### DIFFERENTIAL DIAGNOSIS

DR. EDWARD L. YOUNG: This is a case in which we must discuss the differential diagnosis of a tumor of the midsigmoid causing partial obstruction. The possible causes are many, the probable causes few. This patient had a fairly normal bowel habit, no changes being apparent in the stools except for the presence of blood, so that we can almost surely throw out any ulcerative form of colitis. The things that must be considered in the order of probability are: cancer and diverticulitis, infectious granulomas and the rare tumors, such as sarcoma or some form of benign tumor, such as lipoma. Also, we might consider intussusception as a mere possibility. Although chronic intussusception does exist, it is generally of the ileocolic variety, it is very rare at this age, and its presence does not cause bright blood, so that I think we can discard that diagnosis. Tuberculosis is a possibility. To make us consider tuberculosis is the fact that the x-ray examination showed old tuberculosis in the patient's lung. Tuberculosis of the bowel is usually a disease of young people. Furthermore, tuberculosis usually involves the ileocolic region, and is generally, though not necessarily, accompanied by a certain degree of activity of the pulmonary tuberculosis. In this case, the disease was on the left; it was not the ulcerative but the hyperplastic type because of the tumor

felt. I believe that we can discard tuberculosis. Because of their rarity, we need not consider infectious granulomas of other origin.

The case boils down, then, to a differential diagnosis between carcinoma and diverticulitis, both of which could fit the picture. We used to be taught that patients with diverticulitis rarely bled and that when either gross or microscopic blood was present we should always look for some other disease. However, we now believe that at least 20 per cent of the patients with diverticulitis do bleed at some time or other, although it is not common to have so much bleeding as this patient had. Moreover, a subacute perforation with an infectious area about the bowel could cause such a tumor as that felt in this case, and we do know that diverticula were visible on the x-ray films. Carcinoma, of course, can fit this picture very well. We must remember, moreover, that both could exist in the same case. I believe, however, that when this is so there is no connection between the two. Is it possible, then, to differentiate these two lesions? I think that the x-ray films are the best evidence we have, and I should rely largely on what the radiologist says. If the statement "slightly intussuscepting" means anything, it certainly suggests a proliferative type of growth of the inside of the bowel. What about it, Dr. Hampton?

DR. AUBREY O. HAMPTON: I think the report reads a little more obviously like tumor than the films do. In the large one, practically everything is obscured by what appears to be diverticulitis, and there is a good deal of spasm in the sigmoid. This second film must be the one from which they concluded that the mucosa was abnormal. The area of involvement is only about 3 or 4 cm. I think this may be what they meant by the intussuscepting defect, but I do not believe that we have any evidence of intussusception. We have evidence of diverticulitis and absence of mucosa over a distance of 4 cm., with an apparent filling defect.

DR. YOUNG: Should you be willing to make a diagnosis on the x-ray films as they stand?

DR. HAMPTON: I think I should, with a little reservation.

DR. YOUNG: If we may believe that diagnosis, what is the treatment? With the two in our mind, the main thing to do is treat it as cancer because I do not believe the surgeon exists who can feel of this with his hand in the abdomen and be sure which it is. Therefore, it must be treated as a cancer. In this seventy-year-old man, the blood pressure was 240, and the justification of any operation is that the hazard of operation, in the last analysis, is no greater than that of the condition one is operating for; the outcome, if the

condition is cancer, is certain death. So that or is justified in going the distance. I believe the evidence points more strongly to cancer than to diverticulitis.

DR. REED HARWOOD: Did the laboratory tests show occult blood in the stools?

DR. TRACY B. MALLORY: Yes; on the single specimen examined.

DR. CHESTER M. JONES: It certainly is most unusual to have that much blood from diverticulitis, although one does see some blood occasionally.

DR. MALLORY: One interesting sidelight is that during the entire period covered by this story the patient was being treated in our tumor clinic for carcinoma of the cheek. He never told anyone in this hospital, however, about the abnormality of his stools. He went to another hospital with that story, and the first x-ray examinations were done there and were negative.

DR. YOUNG: Do you mean that they did not spot the diverticula?

DR. MALLORY: So the report says. It is hard to believe.

DR. HAMPTON: I do not believe that they missed them.

DR. HARWOOD: It seems unusual to have a normal red-cell count and hemoglobin with bleeding for thirteen months.

DR. CLAUDE E. WELCH: The patient was not the most intelligent Irishman I have seen, and we doubted much of the story. There is no question that he bled a good deal, however. We thought he had carcinoma of the colon on the basis of the first x-ray report. But, in view of the visible diverticula, we had enough doubt about the situation to do a second barium enema, twelve days after the first, to determine whether there had been any change. The report that came back from that was "absolutely no change," and we justifiably thought that we had additional evidence in favor of the existence of two lesions—diverticulitis and carcinoma. At the time of the second operation, it was noticed that the patient had a tremendous mass of adhesions in the lower pelvis, large enough for us to be tempted to say that the lesion was inoperable. With a little difficulty, the lesion was resected, and anastomosis done. The patient had a perfectly uneventful postoperative course.

DR. HAMPTON: The way the case is building up, I am sure that Dr. Young and I will be wrong. The films, however, certainly suggest that the patient had a carcinoma.

DR. YOUNG: I was going to ask if you would "stick your neck out" too.

DR. HAMPTON: I looked at all the films and did not think of it until I saw the last spot film,

which looks very much like carcinoma. The other films look like diverticulitis.

DR. YOUNG: The question of whether the mucosal layer was gone is important, and I assumed you said it was.

DR. HAMPTON: It appeared to be. I cannot be certain. One can have edema or constriction from outside pressure or infection, and the mucosa will appear to be abnormal.

DR. YOUNG: Did you feel the mass at the time of the first operation?

DR. WELCH: No attempt was made to palpate it at the time of cecostomy.

#### CLINICAL DIAGNOSIS

Carcinoma of sigmoid.

#### DR. YOUNG'S DIAGNOSIS

Carcinoma of sigmoid.

#### ANATOMICAL DIAGNOSIS

Diverticulitis of sigmoid.

#### PATHOLOGICAL DISCUSSION

DR. MALLORY: The resected specimen showed multiple diverticula, several of which were inflamed. There was no evidence of tumor. The mucosa between the diverticula was markedly edematous, producing a pseudo-polypoid appearance, which accounts for the abnormal mucosal pattern in the films.

DR. HAMPTON: Was there an abscess?

DR. MALLORY: No frank abscess.

DR. HAMPTON: No perforation?

DR. WELCH: No.

### CASE 28172

#### PRESENTATION OF CASE

*First admission.* A fifty-six-year-old housewife was admitted to the hospital because of cramping lower abdominal pain and vomiting.

The patient had been constipated for many years and on occasion used various laxatives, but she had no pain or other symptoms referable to the bowels. Three days before entry, following an upper respiratory infection of several days' duration, there was a fairly sudden onset of severe cramping pain, extending across the lower abdomen from the right lower quadrant. The patient took a proprietary laxative and vomited almost immediately. Several additional doses of the medicine were then taken, with subsequent partial abatement of the cramps. On the day preceding admission, there was further vomiting, and the cramping became severer despite further doses of laxatives

and hot rum punch. On the first day of the illness, the patient had two or three bowel movements, on the second day one or two, on the third day four, and on the day of admission none. None of the movements included evident blood.

Six years before entry, the patient had a complete hysterectomy, a bilateral salpingo-oophorectomy and an appendectomy performed at another hospital, with the finding of leiomyomas of the uterus, chronic cervicitis and bilateral early cystadenomas of the ovaries. Four years later, mastectomy was performed in the same hospital, in treatment of a benign intractable papilloma. The next year, the patient had a sacral laminectomy at this hospital because of backache and swelling over the lower spine. Two paradural cysts of unknown type were drained, but not removed or biopsied. Aside from these difficulties, the patient was in good health.

On admission, the patient appeared well nourished but acutely ill, with flushed face, dry, coated tongue and warm skin. The nose and throat were mildly injected. The lungs were clear. The heart was normal. The abdomen was distended, with hypoactive peristalsis. An area of erythema over the left lower quadrant suggested a burn from a hot-water bottle. There was generalized abdominal tenderness, most marked in the left lower quadrant, where voluntary rigidity was also most marked. There was rebound tenderness all over the abdomen, which was referred to the point in the left lower quadrant that was most tender on direct pressure. Pelvic examination showed boggy induration of all sides of the vagina, without definite masses. Tenderness was somewhat more marked on the left. Rectal examination showed induration high on the anterior wall of the rectum.

The blood pressure was 140 systolic, 80 diastolic. The temperature was 103°F., the pulse 100, and the respirations 20.

Examination of the blood showed a white-cell count of 15,050, with 80 per cent hemoglobin. The urine was normal. The blood chemical findings were essentially normal.

On the fifteenth hospital day, a roentgenogram of the large bowel showed prompt filling of the rectum and distal sigmoid. At the junction of the middle and proximal thirds of the sigmoid, there was a more or less annular area of narrowing, conical in its distal portion, causing almost complete obstruction. There was no definite edge to this lesion, suggesting an extrinsic pressure defect. A small pouch just above the area of narrowing was consistent with a small diverticulum.

On the twenty-fourth hospital day, a Devine colostomy was performed. Exploration of the abdomen showed a mass in the pelvis apparently



continuous with the sigmoid, which felt irregular, edematous and fixed. Adhesions were present in the region of the old laparotomy scar. There was no evidence anywhere of metastatic disease. Following operation, there was some fever, which slowly subsided. The patient was discharged on the twenty-fourth postoperative day, with the colostomy working well.

*Second admission* (eleven months later). The patient continued well, following discharge. There was no pain, fever, cramping or rectal bleeding. A follow-up roentgenogram showed obstruction of the sigmoid, quite similar to that noted in the previous examination. Barium introduced through the colostomy opening into the distal segment of the colon passed readily to the area of obstruction, outlining a few small diverticula just proximal to the obstruction.

On re-entry, physical examination was essentially as before, except that the abdomen was free from tenderness and distention. The rectum admitted a proctoscope to a distance of only 13 cm., owing to angulation of the bowel. The mucosa appeared edematous, injected and friable.

Examination of the blood showed a white-cell count of 8800. The blood chemical findings were normal.

An intravenous pyelogram was negative.

On the fifth hospital day, an operation was performed.

#### DIFFERENTIAL DIAGNOSIS

DR. HENRY H. FAXON: I can save considerable time by referring to the discussion that Dr. Young has just given. Here, again, we have a differential diagnosis of a lesion in the sigmoid with the same possibilities that he has already mentioned. Before I heard the final outcome of his problem, I had planned to emphasize what Dr. Jones has said: that bleeding is most uncommon with diverticulitis. On the basis of the bleeding in the preceding case, I should have been extremely skeptical that the lesion was due to diverticulitis.

My discussion of this case is based on the same premise that the absence of gross blood is suggestive of a diagnosis of diverticulitis. The disease that the patient apparently now has is obviously in the sigmoid. The outstanding points, it seems to me, are that the two acute episodes were of short duration, that especially the first of these was marked by the manifestations of infection with an elevated temperature and so forth, and that nearly a year elapsed between the two hospital entries. Let us see now if the X-ray Department can help us.

DR. AUBREY O. HAMPTON: The picture suggests something surrounding the bowel at the point of

maximum narrowing. I believe that the mucosal folds are intact. They could be absent on one side, but I shall stick to the record that the lesion was probably extrinsic and that a diverticulum was present.

DR. FAXON: A possible undetected endometriosis affords the only connection between the present lesion and that for which the previous hysterectomy was done. It is not uncommon to find the large bowel involved in endometriosis, but since the ovaries had been taken out at the time of the operation six years previously, it would be surprising if endometriosis played any part in the present involvement of the large bowel. We have definite information from the operative note that seems to exclude cancer. If a malignant lesion was present, it was at any rate unrecognized by the operator. Furthermore, eleven months went by before the patient again appeared with the same symptomatology and the same type of picture.

What the operation for paradural cyst was and what significance can be attached to it, I frankly do not know. I do not believe that it played a part in the present bowel disease, but I may be overlooking a good lead in merely dismissing it.

I believe that one of the diverticula actually ruptured and gave rise to infection about the bowel, and that with the sidetracking afforded by the Devine colostomy the inflammation quieted down. Many such inflammatory masses are hard to distinguish from cancer at operation, as Dr. Young has said. They often subside but, if due to diverticulitis, often recur in similar fashion. I believe that the primary lesion in this case was diverticulitis.

DR. HAMPTON: What was the X-ray Department's conclusion?

DR. TRACY B. MALLORY: They did not say anything more than "inflammatory mass." It is probably safe to assume that they were thinking of diverticulitis.

DR. HAMPTON: That is the implication I meant to leave.

DR. CLAUDE E. WELCH: Is that not very unusual for that length of time?

DR. HAMPTON: It seems that diverticulitis should have improved more than this patient's had.

DR. WELCH: Especially with colostomy.

DR. HAMPTON: And especially since, at the first examination, the bowel looked somewhat flexible. It did not look like the chronic scarring of diverticulitis.

DR. HOWARD ULFELDER: I performed the first operation in this hospital, and of course responsibility for diagnosis could not rest on that procedure.

It was done merely to defunction the large bowel. I thought I overstepped myself at the time in exploring the patient as much as I did, in view of the very recent pelvic sepsis. However, I did exclude cancer to the best of my ability. I found a well-fixed mass in the pelvis and a normal liver, and then did a transverse colostomy.

#### CLINICAL DIAGNOSIS

Diverticulitis of sigmoid.

#### DR. FAXON'S DIAGNOSIS

Diverticulitis of sigmoid.

#### ANATOMICAL DIAGNOSES

Carcinoma of sigmoid.

Chronic inflammation, with abscess formation in mesentery.

#### PATHOLOGICAL DISCUSSION

DR. MALLORY: At the second operation, the findings were quite different. At that time, it was obvious that the pelvis was quite well filled with carcinoma. It was also clear that the disease was incurable; however, it was decided that enough relief of symptoms could be obtained by resection to justify such a procedure. There was an inflammatory mass in the mesentery, and to a considerable extent the conclusions of the radiologist were justified; but it was a carcinoma, not a diverticulum that had undergone a subacute perforation.

DR. HAMPTON: How big was the carcinoma?

DR. MALLORY: It was an annular lesion about 3 cm. in diameter.

DR. HAMPTON: I cannot find it in the x-ray films.

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established in 1828

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND  
PUBLISHED UNDER THE JURISDICTION OF THE  
COMMITTEE ON PUBLICATIONS

Official Organ of

THE MASSACHUSETTS MEDICAL SOCIETY  
and

THE NEW HAMPSHIRE MEDICAL SOCIETY

## EDITORIAL BOARD

Joseph Garland, M.D.	Stephen Rushmore, M.D.
William B. Breed, M.D.	Henry R. Viets, M.D.
George R. Minot, M.D.	Robert M. Green, M.D.
Frank H. Lahey, M.D.	Charles C. Lund, M.D.
Shields Warren, M.D.	John F. Fulton, M.D.
George L. Tobey, Jr., M.D.	A. Warren Stearns, M.D.
C. Guy Lane, M.D.	Dwight O'Hara, M.D.
William A. Rogers, M.D.	Chester S. Keefer, M.D.

## ASSOCIATE EDITORS

Thomas H. Lanman, M.D.	Donald Munro, M.D.
Henry Jackson, Jr., M.D.	

Walter P. Bowers, M.D., EDITOR EMERITUS

Robert N. Nye, M.D., MANAGING EDITOR

Clara D. Davies, ASSISTANT EDITOR

SUBSCRIPTION TERMS: \$6.00 per year in advance, postage paid, for the United States (medical students, \$3.50 per year); Canada, \$7.04 per year, Boston funds; \$8.52 per year for all foreign countries belonging to the Postal Union.

MATERIAL for early publication should be received not later than noon on Friday.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston, Massachusetts.

## MALPRACTICE INSURANCE FOR PHYSICIANS IN MILITARY SERVICE

A LETTER in this issue of the *Journal* brings up the question whether a physician in military service should carry malpractice insurance.

In an editorial, "Malpractice Actions against Army Medical Officers and Examining Physicians for Local Selective Service Boards," in the September 13, 1941, issue of the *Journal of the American Medical Association*, it was stated that the Judge Advocate General of the United States Army had ruled, on May 1, 1941, that members or prospective members of the Army are entitled to the same civil rights of action between one another with reference to suits for malpractice or negligence as they would have in civil life. Hence, a man in military service who has been

attended by a medical officer in line of duty or a selectee who has been examined by a physician attached, either in a civilian or military capacity, to a selective-service or induction board may bring suit for alleged malpractice. Although no official statement has been offered by the Judge Advocate General of the United States Navy, it seems likely that the same ruling would be made. Furthermore, several of the commercial companies that offer malpractice insurance have recently announced a new type of policy, which covers physicians who are in military service.

Whether this type of insurance is necessary is a matter that each medical officer must decide. It is obvious that all physicians who serve in a civilian capacity on selective-service or induction boards are protected against malpractice suits if they carry standard policies, — and if they are not insured, they are running no more risk than they do in everyday practice. In addition, the chance that suit will be brought by a man in active military service is exceedingly unlikely, — as shown by the relatively low rate of the military policy, — and if action is taken, it has been the custom to transfer the case to a federal court and to furnish the defendant with federal counsel designated by the Department of Justice. In spite of the fact that there is, at present, no legal provision for the Government to pay the claim or to reimburse the defendant if a judgment favorable to the plaintiff is rendered, at least one branch of the service — the Selective Service System — has intimated that it would make an attempt to protect him from financial loss, even if this required a special act of Congress. Although the possibility of personal loss by a well-trained medical officer seems extremely unlikely, the risk does exist and should probably be covered by a military policy.

## THE KENNY METHOD OF TREATMENT OF INFANTILE PARALYSIS

Miss Elizabeth Kenny, a nurse from the hinterland of Australia, developed a treatment for poliomyelitis that is now being widely used in this country. She has carried on her work in America

under the auspices of the National Foundation for Infantile Paralysis, having demonstrated her method before a qualified group of observers at the University of Minnesota. The reports now available suggest that the results of her treatment of patients both in the acute and in the chronic stage of poliomyelitis are unusually satisfactory. In many cases, she has prevented the development of contractures and deformities, and in general, the muscles of these patients have shown less than the usual amount of paralysis. In other words, most observers who have visited the clinic established in Minneapolis have come away impressed by the results obtained. In view of the success of her treatment, plans are being made to publish the essential facts, as well as a discussion of Miss Kenny's ideas, in a pamphlet to be issued by the National Foundation for Infantile Paralysis. Until this is available, those who are interested should consult Miss Kenny's book.\*

Her account, however, is difficult to understand, since many of her arguments require definitions of the terms that she uses. For instance, the word "spasm" is used in a manner foreign to current medical understanding. She speaks of spasm as a primary symptom of paralysis, and considers fibrillation, twitching, hyperirritability to stretching and a tonic state of contraction to be signs of spasm. She believes that spasm is responsible for the paralysis and also for the malposition of the limbs. Flaccid paralysis as a primary symptom of the disease is denied by Miss Kenny, she contends that muscles cannot move, not because they are paralyzed, but because they are overstretched by the opposing group of muscles in spasm. Miss Kenny uses two other confusing terms, "inco-ordination" and "mental alienation." Inco-ordination, according to the interpretation, depends on muscle spasm and is the result of the spreading of impulses to other muscles because the muscle involved exhibits pain or is unable to move. Inco-ordination may also be caused by ineffective contractions in the affected muscles. Mental alienation, the third term, deals with the inability

of muscles to function because of the spasm and pain due to the contraction of opposing groups or because of the interruption of pathways from processes in the central nervous system not permanently destroyed. These three terms, as will readily be appreciated, are almost foreign to medicine, and without Miss Kenny's definitions of them, one cannot even attempt to understand her method and reasoning.

Whatever the theoretical considerations concerning Miss Kenny's work, there can be little doubt of the practical value of her treatment. Although not particularly easy to understand or simple to carry out, the method can be learned in a year by any well trained physician or physiotherapist. It consists essentially of continuous attention from a highly trained staff of attendants, with the absence of manipulation, all appliances or any form of treatment that will increase the spasm in the affected muscles. Massage in all forms should be avoided. Pressure from the bedclothes, unnecessary handling and pressure from casts and splints, according to Miss Kenny, increase spasm. The spasm itself is treated by hot fomentations applied in a careful and routine manner. Moreover, she does not believe in the testing of muscle strength in acute poliomyelitis, since these determinations tend to increase spasm and pain and therefore to retard recovery. When pain and spasm have been overcome by hot fomentations, active therapy is started. The techniques of muscle re-education developed by Miss Kenny call for an intimate knowledge of muscle anatomy and function. Thus, the excellent end results seen in her cases are brought about through careful treatment by use of physiotherapy of a specialized nature directed toward inco-ordination and alienation, as well as through the proper application of heat during the stage of spasm.

The Kenny method completely revolutionizes modern ideas regarding the treatment of acute poliomyelitis. Muscle testing, splinting, avoidance of overstressing, absolute rest and many other procedures are largely overthrown, and additional modifications will naturally follow.

\*Kenny E. *The Treatment of Infantile Paralysis in the Acute Stage*. 285 pp. Minneapolis and St. Paul: Bruce Publishing Company, 1941.

If the technic is adopted, the physician, whether he is a pediatrician, orthopedist, neurologist or clinician, must begin treatment of the affected muscles on the very first day of the disease: in most cases this means starting intensive therapy in a hospital for infectious diseases. Furthermore, treatment must be continued unremittingly until all power that is possible returns to the affected muscles.

## MEDICAL EPONYM

### OPPENHEIM'S SIGN

Hermann Oppenheim (1858-1919), of Berlin, presented a discussion, "Zur Pathologie der Hautreflexe an den unteren Extremitäten [On the Pathology of the Skin Reflexes in the Lower Extremities]," in the *Monatsschrift für Psychiatrie und Neurologie* (12: 421-423, 1902). A portion of the translation follows:

If the handle of the percussion hammer is drawn down along the inner aspect of the lower leg (about at the posterior margin of the tibia or even beyond it) in healthy persons, there will be seen either no motion of the foot and toes, or a plantar flexion. . . . In patients presenting the symptom complex of spastic paraplegia or hemiplegia, the maneuver described usually results in a reflex muscular contraction causing an extension of the great toe, and either adduction or abduction of the foot.

R. W. B.

## MASSACHUSETTS MEDICAL SOCIETY

### COMMITTEE ON MATERNAL WELFARE

CASE HISTORY: HYDRAMNIOS FOLLOWED BY POST-PARTUM HEMORRHAGE, HYSTERECTOMY AND DEATH

A thirty-seven-year-old essential primipara (there had been one spontaneous abortion) who had had excellent prenatal care developed an upper respiratory infection for which she was hospitalized at the very end of her pregnancy. There undoubtedly was some mistake concerning dates, since the record states that labor did not set in until five weeks after the estimated date. There had been no complications during pregnancy; the blood pressure and urine were normal, and the past history was irrelevant. A diagnosis of hydramnios and anencephalus was made before labor. Although it is not so stated, an x-ray film had in all probability been taken on which this diagnosis was based. The upper respiratory infection was not accompanied by fever. Labor

started spontaneously by the rupture of the membranes, and eighteen hours later the patient was delivered normally, with the aid of cleidotomy. The weight of the baby is not given, but presumably it was a large child. A second-degree tear of the perineum was sustained and immediately repaired. The placenta, delivered normally, was followed by tremendous hemorrhage, and the uterus was packed. The patient was given four transfusions. Since the uterus continued to bleed, an abdominal suprapubic hysterectomy was performed eight hours after delivery. In spite of three additional transfusions, death occurred twelve hours later. No autopsy was performed.

\* *Comment.* Hydramnios, with the resulting overstretching of the uterus, has always been considered a possible cause of post-partum hemorrhage. For the same reason, the stretching that accompanies twin pregnancies may also result in bleeding. In all such cases, the fundus should be very carefully watched after delivery; sometimes the intravenous use of ergotrate is of value in combating atony. All that could possibly have been done for this patient was done. The fatality merely emphasizes the occasional seriousness of post-partum hemorrhage and the ever-present possibility of the need for hysterectomy and for repeated transfusions.

### DEATHS

CRANE — CLARENCE CRANE, M.D., formerly of Boston, died April 13. He was in his seventy-second year.

Born in Salem, Oregon, Dr. Crane received his degree from Boston University School of Medicine in 1900. He was assistant professor of surgery at Boston University School of Medicine from 1900 to 1921, and staff surgeon of the Massachusetts Memorial Hospitals. He was a former member of the Massachusetts Medical Society and the American Medical Association, and a fellow of the American College of Surgeons.

He is survived by his widow, three sons, and two daughters.

PERRY — SHERMAN PERRY, M.D., of Winchendon, died April 20. He was in his sixty-fourth year.

A native of Passaic, New Jersey, Dr. Perry received his degree from Harvard Medical School in 1907. He served on the staffs of the Worcester City, Boston Children's and Tewksbury State hospitals and was a former president of the Worcester District Medical Society. He was a member of the New England Obstetrical and Gynecological Society, and a fellow of the American Medical Association.

His widow survives him.

WALKER — JOHN B. WALKER, M.D., formerly of Boston, died April 13. He was in his eighty-third year.

Dr. Walker received his degree from Harvard Medical School in 1888. He was formerly on the staff of the Boston City Hospital and was a fellow of the Massachusetts Medical Society and the American Medical Association.

He is survived by his widow, two sons and two daughters.

## WAR ACTIVITIES

## CIVILIAN DEFENSE

HOSPITALS TO BE REIMBURSED FOR CARE  
OF CIVILIAN CASUALTIES

Payment for temporary hospitalization of civilians injured as the result of enemy action has been made possible by a recent agreement between Administrator Paul V. Nitte of the Federal Security Agency and Director James M. Landis of the Office of Civilian Defense. The funds have been allocated to the United States Public Health Service by the Federal Security Administrator from funds made available to him from the President's emergency fund. A joint memorandum embodying the details of the program has been issued by Surgeon General Thomas Parran of the United States Public Health Service and Dr. George Brehm, chief medical officer of the Office of Civilian Defense.

The plan provides that all hospitals caring for civilian casualties in the event of air raids or other enemy action will be reimbursed by the federal government at a rate of \$175 a day. This is the rate of reimbursement established by the Federal Board of Hospitalization for federal beneficiaries in government hospitals and may be changed as conditions require, it was stated.

Any hospital in the Nation, voluntary or governmental, may be used as a casualty receiving hospital in the Emergency Medical Service established by the Medical Division of the Office of Civilian Defense. In addition certain hospitals and other institutions in safe areas may be used as emergency base hospitals for casualties or other patients whom it may be necessary to evacuate from urban hospitals in exposed areas. The new agreement provides that federally owned equipment may be loaned to the base hospitals and that their staffs will be supplemented by physicians of the region who will be commissioned in the reserve corps of the United States Public Health Service. It is emphasized that management and control of all hospitals, both local casualty receiving hospitals and emergency base hospitals, will remain the responsibility of the local or state authorities.

In the establishment of emergency base hospitals, emphasis will be placed on the relative safety of the area and the availability of existing hospitals and other institutions. Hospitals are now being surveyed for this purpose and will be classified on a basis of size, equipment and standards of operation.

It is proposed to begin immediately the organization of medical staffs for future base hospitals as hospital units affiliated with casualty hospitals similar to the affiliated general hospitals of the Army. The physicians, surgeons, specialists and dentists who are to be commissioned in the Public Health Service Reserve for service in these hospitals will receive rank, pay and allowance equivalent to those of the Medical Corps of the United States Army. They will be selected from older age groups, from physicians with disabilities that make them ineligible for military service and from women physicians. So far as possible, they will be assigned to service in the regions in which they live. Because they are to function as balanced professional staffs, they will be recruited from the staffs of civilian hospitals and cleared through the Procurement and Assignment Service.

## MISCELLANY

TUBERCULOSIS IS FOUND  
WHEN LOOKED FOR

The gap between proved knowledge and effective action based on that knowledge is nowhere more glaring than in our fumbling efforts at control of the commonest of the infectious diseases.

We know that the time lost from the common cold would build hundreds of the planes we now need so much. Yet, the simple prophylactic measure of isolating all those with colds in early stages is applied routinely to a few school children only.

This failure to co-ordinate knowledge and action is also all too common in our efforts to control and eradicate tuberculosis.

That tuberculosis can be found and is most easily cured in the stage before symptoms appear is an axiom that has grown true with repetition, yet the great majority of people fail to translate this into the action that will safeguard themselves and their families from this disease.

But what are the facts? In four years, the deaths from tuberculosis surpass the number of those killed in all the wars the United States has ever fought. If the losses of one year from tuberculosis could be attributed to enemy action, the nation would be shocked with grief and vow vengeance at any cost. Yet the slow undramatic dribbling away of lives goes on day by day, although proof has been added to proof that this can be stopped.

An example is provided by colleges and universities. Into their doors every fall go hundreds of thousands of American youth, those favored ones of earth from whose ranks come most of the trained men and women of our society. Yet tuberculosis has already laid its hand on many of these. During 1939-40, according to the report of the Tuberculosis Committee of the American Student Health Association, published in the *Journal Lancet*, 637 cases of tuberculosis were found in two hundred and forty-eight of these institutions with a total enrollment of 500,000 students, because it was looked for. Most of these infected students can be saved for useful, productive lives with a minimum of time lost.

What is the story where the college authorities report that no search is made? The fact that only 35 cases appeared in two hundred and twenty-seven institutions among 200,000 students during the same period provides the answer. But is that the whole story? No, for back of those 35 cases many more stand in shadowed ranks, already touched by the destroyer. It is easy to prove that tuberculosis is there—a tuberculin test, followed by an x-ray film of positive reactors, is the magic wand that will bring to light the hidden lesions. But when they are not found early we know the story too. Most of them progress to the stage where treatment is to be reckoned in years, and complete cure is the exception.

And what of the four hundred and two institutions whose administrators did not even reply to the questionnaire? One can only surmise that they, too, have failed to translate the thing they know into the thing they do. Some of them, perhaps, are even unaware that tuberculosis is now, as it has always been, a foe of youth.

Yet it is to the pursuit of knowledge that all these institutions are dedicated and it was many years ago that Ralph Waldo Emerson said: Education is not pouring knowledge into minds; it is not erudition. A person is not truly educated unless knowledge influences his

doing as well as his *thinking*. Insofar as learning alters and directs *behavior* it is education."

In this respect, unfortunately, educators follow but the common path. In the trade union, the insurance office and the department store, in the hospitals and the homes for the aged, wherever men and women are gathered together, tuberculosis may be found when looked for. No class is exempt; no land is free from it—it is an enemy power we know how to conquer, but the war is prolonged by "too little and too late."—Reprinted from *Tuberculosis Abstracts*, April, 1942.

## CORRESPONDENCE

### MILITARY MALPRACTICE INSURANCE

*To the Editor:* I wish to call to the attention of all physicians entering the armed services of the United States or serving as examining physicians for local selective-service boards that they may be sued by selectees, or by anyone in the armed services of the United States, treated by the medical officer, on an allegation of malpractice. This ruling, dated May 1, 1941, was made by the Judge Advocate General of the United States Army.

Military policies, available on and after April 10, 1942, provide \$2500 to \$7500 limits for \$10.00 a year. These policies are issued by the insurance companies solely for malpractice insurance covering physicians in military service. If any income is derived by the medical officer on active military service from association or agreement with a physician in private civilian practice, the military policy does not apply. If a medical officer desires a military policy, he must certify that he was a member of his state medical society or association when inducted into the service.

Medical officers discharged from the armed services and entering practice again should remember to reinstate their regular malpractice insurance policies for protection in civil life, if they desire such protection.

WILLIAM REID MORRISON, M.D.

520 Commonwealth Avenue  
Boston

## REPORTS OF MEETINGS

### NEW ENGLAND PATHOLOGICAL SOCIETY

A regular meeting of the New England Pathological Society was held on November 20, 1941, with Dr. B. Earle Clark presiding. Dr. William Dock, professor of pathology at Cornell Medical College, spoke on "The Kidneys and Hypertension."

Scarring or compression of the kidneys and partial occlusion of the renal artery or of the aorta proximal to the renal artery leads to sustained hypertension, and since this persists for hours after removal of the kidney it cannot be due to a reflex; it might be caused by decreased liberation of an antipressor substance or release of a pressor hormone, which seems likelier, since total nephrectomy does not cause a rise in pressure. All attempts to demonstrate a vasoconstrictor substance in renal hypertension have failed; indirect evidence from studies of flow in the limbs does not prove that such a substance is present in human patients and rules it out in the transient hypertension of acute glomerulonephritis (Pickering). Dr. Dock and his collaborators have found no difference in the pressure levels of control and renal hypertensive rats, rabbits and dogs, after destroying the central nervous system. Pithed animals are very sensitive to vasoconstrictor substances, including renin, and it is

therefore concluded that the renal pressor hormone acts by changing the set of the vasomotor center, and not directly on arterioles.

Perfusion of kidneys post mortem and x-ray films of the injected renal arterial bed prove that an organic increase in resistance to renal blood flow is not usual in hypertensive patients without uremia; narrowing of the main artery is even rarer. In most cases, the kidney shows, in addition to atheromatous narrowings, arteriolar change equal to that in the other kidney, whereas in Goldblatt-clamp hypertension, little or no change is present in the kidney protected by the clamp even though marked change occurs in the retinal vessels and in the opposite unprotected kidney. Accordingly, Dr. Dock considers most narrowed main renal arteries to represent late complications, not primary causes. There is strong evidence, based on the evolution of vascular disease in the eyegrounds and on studies of Goldblatt hypertension and pulmonary arterial sclerosis, that hypertension may cause or accelerate atherosclerosis and arteriolar degeneration. Therefore, it is most probable that renal sclerosis is a result, not a primary cause, of so-called "benign" hypertension. At present, it seems probable that inherent vasomotor instability or adrenocortical disease underlies many cases of arterial hypertension, and that the tendency to vascular degeneration inherited by some people leads to rapid renal, retinal, cerebral or coronary arterial disease if they become hypertensive. Others, especially women, have inherent soundness of the vascular tree, and after decades of hypertension show minimal damage.

Rodents, dogs, cats and men have easily recognized peculiarities of the first loop of the distal convoluted tubule (macula densa) and of the wall of the afferent arteriole. No definite change in this tissue is seen in most human hypertensive patients (benign, glomerulonephritic or pyelonephritic coarctation of aorta), or in rats, rabbits and dogs in which hypertension has developed slowly and gradually; changes have been seen by others in many types of renal hypertension in animals, and Dr. Dock has observed hyperplasia and swelling of the cells of the afferent arteriole in dogs with rapidly developing hypertension and has been much struck by the hypertrophy and fuchsinophilic granules in the arterioles of the hypertensive cat (Graef). He has also been struck by the severe damage to this tissue in amyloid disease, and suggests that the absence of hypertension in most amyloid uremic cases is due to the fact that the specific cells have been replaced by amyloid. However, it must be noted that uremia in amyloidosis often develops rapidly and may be due to an extremely severe damage to the adrenal cortex. Dr. Dock found excellent renal perfusibility in one case of amyloid disease with uremia. Careful study of amyloidosis, with and without hypertension and during life as well as post mortem, may prove valuable in correct judgment of the role of the juxtaglomerular tissue. The morphologist, whose observations usually start most clinical problems, may be able by refined technics in pedigreed cases to solve a complicated situation.

In the discussion, neither Dr. Soma Weiss nor Dr. Alan Moritz considered the evidence presented by the speaker sufficient to rule out the renal origin of hypertension. Dr. Weiss believed that the evidence drawn from the pithed-animal experiments was not foolproof, since it is known that vasoconstrictor substances may act differently under various conditions. Dr. Moritz stated that the possible causal relation of renal arteriolar disease and hypertension is still an open question.

# HARVARD MEDICAL SOCIETY

A regular meeting of the Harvard Medical Society was held at the Peter Bent Brigham Hospital on December 9, with Dr Soma Weiss presiding.

The case presentation was that of a forty-one year-old woman whose history dated from an attack of acute otitis media eleven months prior to admission. There were recurrent episodes of draining from the ears for three months followed by a period of one month without symptoms. Then began a train of manifestations including fever, chills and night sweats. Four blood cultures were found to be positive for *Streptococcus viridans*. Sulfadiazine therapy was instituted, and the patient also received several administrations of typhoid vaccine. This treatment was temporarily discontinued when she had what appeared to be a subarachnoid hemorrhage. During this therapy, there was great clinical improvement in November, however, her chills, fever and night sweats recurred and blood cultures were again positive. Sulfadiazine therapy was reinstituted, with clinical improvement again. One important point brought out in the discussion of this case was that crude liver extract or crude preparations of the vitamin B complex should not be administered when the sulfonamides are being employed, apparently the aminobenzoic acid responsible for the inactivation of these drugs is present only in the crude forms.

The speaker of the evening was Dr Henry A. Christian whose subject was "Glomerular Lesions of Subacute *Streptococcus Viridans* Endocarditis." This study was based on 11 patients at the Peter Bent Brigham Hospital with this disease. The gross descriptions were taken from the records, whereas the microscopic descriptions and conclusions are those of the speaker. It was interesting that in the gross these kidneys revealed the typical flea bitten appearance in only 13 per cent of cases. A moderate amount of edema and swelling was a common finding, on the other hand. Ninety per cent of the organs had infarcts microscopically, and 25 per cent of these were not noted grossly. It was concluded, therefore, that this already high percentage might have been even higher if better sections had been chosen. A correlation with the clinical record revealed that such infarcts are entirely unpredictable, for they seem, of themselves, to cause no urinary signs and symptoms.

Microscopically, the changes in the tubules are neither striking nor specific nor primary. The changes in the glomeruli, however, are multiple somewhat specific and important. In 80 per cent of the specimens, there was an intracapillary proliferation of cells, which were mostly endothelial but, to some extent, epithelial. This lesion, which is essentially the same as that of diffuse glomerulonephritis, appears to have little if any effect on the measurable kidney functions and causes no appreciable change in the urinary output or sediment. Some of these cells undergo varying degrees of degeneration, with a tendency to granulation of the cells and a decrease in size of the nucleus. Locally, epithelial crescents are found in 36 per cent, with fibrous degeneration of the cells in 26 per cent of specimens. The fibrous crescents may be detached from Bowman's capsule—an indication that degeneration occurs in the fibrous stage. Completely organized glomeruli are occasionally found, are variable in any given patient, and interestingly enough are not found in those with the worst kidney function. Embolic lesions are fairly frequent, but there are few in any given case. They are present in about 40 per cent of the kidneys but were numerous in only 4 cases. Masses of *Streptococcus viridans* organisms are present in approximately 6

per cent of cases. The most frequently encountered lesions macroscopically and microscopically are, respectively, infarcts (90 per cent) and a diffuse cellular proliferation similar to that of glomerular nephritis (85 per cent). Dr Christian believes that the hyaline changes are a manifestation of embolic thrombotic lesions, which are not found in normal glomeruli, contrary to the teaching of some.

Clinically, albuminuria appeared in about 75 per cent of cases, although the same degree of infarction was present in the remainder, hence, infarction cannot be the sole cause of this sign. Casts were found in surprisingly few urinary sediments and were usually of the simple variety. Hematuria was also present in 75 per cent of patients, but was rarely persistent. There were usually recurrent attacks of microscopic hematuria.

Correlation of the clinical and pathological findings reveals that infarcts are not a significant factor, and that embolic thrombotic lesions are not often associated with hematuria. Probably, the most constant association is with focal lesions, especially those of the epithelial crescent type. On the whole, the kidney function remains surprisingly good to the end. In no case in Dr Christian's series did death result from uremia. The phenol sulfonphthalein and urea-clearance tests were usually good, and it was found that infarcts might involve a large portion of the kidney without significantly impairing the function during the life of the patient.

The discussion was opened by Dr James P. O'Hare, who emphasized certain facts brought out by Dr Christian and raised the question of why there is no elevation of blood pressure in this condition, as in chronic glomerulonephritis. Dr Laurence B. Ellis of the Boston City Hospital, in corroborating the rarity of terminal renal manifestations, observed that he had seen only one such case in over five years of observation.

In closing the discussion, Dr Christian stated that the probable reason for the lack of hypertension is the absence of true vascular lesions. The lack of urinary symptoms is probably due to the short course of the disease. Nevertheless, lesions have been found in experimental poisoning with uranium so that they may be considered nonspecific glomerular lesions. And since the lesions found in glomerulonephritis are the same as those caused by the *Streptococcus viridans*, it is possible that the lesions of the former condition are the result of the streptococcus itself rather than an effect of allergy, which is the most widely accepted current belief.

## BOOK REVIEWS

*Malignant Disease and Its Treatment by Radium*. By Strinford Cade, F.R.C.S. 4°, cloth, 1280 pp., with 623 illustrations, many in color. Baltimore: William and Wilkins Company, 1940. \$18.00.

This elaborate study, which gives a comprehensive picture of treatment by radium of cancer, is praiseworthy but outmoded. The swift progress in roentgen ray therapy has so altered the field that as one leafs through these pages one is reminded of the brave but tactically outmoded struggles of the British and French armies against the Panzer divisions. The photographs of wooden helmets for the application of radium to an intracranial tumor, for example, have more value as a medical curiosity than as an aid to the tumor therapist.

The section on the physical aspects of radium is adequate, and the section on the biologic effects of radiation is interesting although somewhat sketchy. The illustra-



tions are clear and well chosen. Some of them are in color.

For the experienced practitioner who has a wide knowledge of the uses and limitations of radium and x-ray therapy in the field of cancer, the book will be of value. For others, although well and honestly written, it cannot but be misleading.

*Bibliographia Primatologica: A classified bibliography of primates other than man. Part I. Anatomy, embryology and quantitative morphology; physiology, pharmacology and psychobiology; primate phylogeny and miscellanea.* By Theodore C. Ruch, B.Sc., Ph.D. With an introduction by John F. Fulton, M.D., Ph.D. 4°, cloth, 241 pp. Springfield, Illinois: Charles C Thomas, 1941. \$8.50.

The use of primates as experimental animals, particularly in the study of the intricacies of the brain, in recent years has resulted in many studies on the animals themselves. Laboratories of primate biology have come into being, bringing new knowledge of the habitats, conditions favorable to transportation, details of sexual life and conditions of breeding. Some types, of great research value, are now being bred for the first time in this country.

With this impetus to study of the primates, the literature, scattered widely in many journals, needed correlation and classification. This Dr. Ruch has done, with bibliographic accuracy, for nearly four thousand separate articles. To the usual reference material are added many facts in abbreviated form: the proportion of the paper given to primate material when other topics are considered; notes on plates, figures, tables and references; and the genera of the animals studied.

This painstaking and finely done piece of bibliographic research is the first book issued under the auspices of the Historical Library of the Yale Medical Library. It augurs well for future publications from this source.

*Leaders of Medicine: Biographical sketches of outstanding American and European physicians.* By Solomon R. Kagan, M.D. 8°, cloth, 176 pp., with 4 illustrations. Boston, Massachusetts: The Medico-Historical Press, 1941. \$3.00.

This volume is in the familiar pattern of Dr. James J. Walsh's *Makers of Modern Medicine*. It consists of a dozen brief biographic sketches of outstanding American and European physicians of the nineteenth century, from Jacob Henle to William Henry Welch. There are engraved portraits of both these men, and of Paul Ehrlich and Jacob Solis-Cohen.

All the biographies are extremely vivid and well documented. The best is that of Sir William Osler, perhaps because he was intrinsically the greatest of the group. Others of almost equal interest, however, are those of Virchow, Mitchell, Jacobi, Allbutt, Billings, Cohnheim and Weigert.

A great debt of gratitude and appreciation is owed to Dr. Kagan as a continuator of the work of Walsh and of Garrison as American medical historians.

*Essentials of Electrocardiography: For the student and practitioner of medicine.* By Richard Ashman, Ph.D., and Edgar Hull, M.D. Second edition. 8°, cloth, 373 pp., with 122 illustrations and 5 tables. New York: The Macmillan Company, 1941. \$5.00.

The second edition of this valuable text will be greeted with interest by all who are familiar with the first. They will find practically a new book incorporating a great deal of material regarding the basic theory of the electrocardio-

gram that has come to light within the last five years. They will also find a much more adequate treatment of the subject of chest leads than was possible in the first edition.

Unlike many textbooks, this volume is stimulating reading because it bears the stamp of originality all the way through and is not merely a summary of the work of others. Although some students of the subject will find points of disagreement, the general presentation leaves little to be desired. To this reviewer, however, it appears that the authors have, on the basis of theory, carried their refinement of electrocardiographic diagnosis a little farther than existing post-mortem correlations warrant. Specifically, one could wish for a more substantial basis than the authors present for interpretation of deviation of the axis of the T waves in clinical terms. Because of the already prevailing tendency of physicians to read too much into the electrocardiogram, this book is to be recommended more to cardiologists of experience than to beginners.

*Essentials of Dermatology.* By Norman Tobias, MD 12°, cloth, 497 pp., with 143 illustrations. Philadelphia: J. B. Lippincott Company, 1941. \$4.75.

The reviewer was amazed at the dermatology contained in this small book, free from the usual verbiage of most textbooks on dermatology. The clinical descriptions are concise, the histopathology contains the necessary details, and the treatment is practical. The classification of the diseases is not confusing, owing to the repetition of entities overlapping in the various sections, when the disease cannot be classified in any one group. The book reflects the author's comprehensive knowledge of the literature, for otherwise he would not have been able to infer essential principles of past and present dermatology. It is noticeable that the little volume includes the most recent studies in dermatology.

The author deals with the treatment of cutaneous diseases in a most practical manner. The prescriptions suggested are not of the shotgun variety, but are sensible in their simplicity, with explanations of the reasons for their use.

The book is legibly printed on good paper, compact and well illustrated. Many of the pictures are excellent; however, at least a third of them, because of poor photography, could be removed without loss. This book is so easily read that it would be no task to the student, and therefore can be recommended to him. It would be very useful to general practitioners and even to dermatologists who desire a quick review of the essentials in their specialty.

*Microbes Which Help or Destroy Us.* By Paul W. Allen, Ph.D., D. Frank Holman, Ph.D., and Louise Allen McBe, M.S. 8°, cloth, 540 pp., with 102 illustrations and 14 color plates. St. Louis: The C. V. Mosby Company, 1941. \$3.50.

This semipopular account of bacteriology covers the entire field, with emphasis on history, public health and the prevention of disease. The story has been told in better form many times before, and it is difficult for the reviewer to see why this book was published. Many of the illustrations are poor and crude. The facts in general are correct, and the book may be safely put in the hands of the public. As a text of particular value, however, it cannot be highly recommended.

# The New England Journal of Medicine

Copyright 1947 by the Massachusetts Medical Society

VOLUME 226

APRIL 30, 1942

NUMBER 18

## A STATISTICAL STUDY OF SIX HUNDRED AND SEVENTY-ONE CASES OF APPENDICEAL PERITONITIS\*

HORATIO ROGERS, MD,† AND HENRY H FAXON, MD‡

BOSTON

### INTRODUCTION

OF all the surgical diseases that engage wide spread interest, appendicitis is undoubtedly the most familiar. It is not surprising therefore that the literature should be so voluminous or that it should cover so many different and almost unrelated aspects.

The present study is confined to the clinical problem of peritonitis in patients brought to the hospital for appendicitis. Between 1929 and 1940, the staff of the Massachusetts General Hospital treated 5055 cases of appendicitis, with a mortality

will often be difficult and their mortality discouragingly high. The present study concerns these cases.

The surgeon's hand has been greatly strengthened by the recent progress in chemotherapy, surgical bacteriology, blood chemistry and intestinal intubation, and it is clear that the mortality rate of appendiceal peritonitis is being reduced by their practical application. Our own, for example, has dropped from 25 per cent in 1929 to 6 per cent in 1939, and similar reductions are being widely reported. However, they are only aids and cannot be substituted for clinical judgment and surgical skill. We have therefore concentrated this study on the clinical factors that can be shown to affect the mortality rate of appendiceal peritonitis.

Peritonitis, within the meaning of this study, consists in the presence of gross perforation, pus in the peritoneal cavity or abscess formation as seen at operation or autopsy or as made clear by the clinical course of the disease. Cases wrongly diagnosed have been excluded. Although the absence of gross peritonitis could easily be recognized at operation, we have found it impossible to determine the exact extent without doing a dangerous and unjustifiable amount of exploration. This experience, in addition to the fact that treatment must actually be planned entirely on the basis of the clinical data available before operation, has persuaded us to abandon the purely pathological classifications so often seen in the literature in favor of a classification based on preoperative clinical findings. Of these, we have taken mass formation to be the most fundamental. The presence of a palpable mass gives indisputable evidence of some degree of localization and hence, at least from the point of view of treatment, serves to separate the group in which localization has already occurred from the group in which localiza-

TABLE 1 Incidence and Mortality of All Cases of Appendicitis

TYPE OF APPENDICITIS	NO. OF CASES	NO. OF DEATHS	MORTALITY
Without peritonitis	4384	1	0.3
Acute	2630	14	0.53
Chronic	154	2	0.11
With peritonitis	671	87	12.9
Acute without mass	444	71	15.99
Acute with mass	227	16	0.5
Totals	5055	103	
Average			2.04

rate of 2.04 per cent, but the mortality rate for the 384 patients without peritonitis was 0.37 per cent, contrasted with one of 12.97 per cent for the 71 patients who did have peritonitis (Table 1). Efforts have been and must still be directed toward the earlier diagnosis and treatment of appendicitis, so that this excessive mortality may be avoided, but at the same time one must recognize the facts that there will always be cases of appendiceal peritonitis, and that their management

\*From the Surgical Services, Massachusetts General Hospital. Read by title at the annual meeting of the New England Surgical Society, New Hampshire, September 5 and 6, 1941.

†Instructor in surgery, Harvard Medical School, Boston, Massachusetts.

‡Assistant in surgery, Harvard Medical School, Boston, Massachusetts. Presently at General Hospital.

tion has not and perhaps will not take place. Because these two groups are readily distinguishable clinically and because the treatment differs basically in each, they are classified and reported separately as Parts I and II of this study.

The objection may be raised that such a classification fails to permit any satisfactory comparisons between our figures and those from other clinics where the figures are based on a strictly pathological classification of cases. Our attempts to derive really comparable mortality figures from various published reports have convinced us of the practical impossibility of taking all the relevant factors into account or even of knowing, in any given report, what they were. The essential factors governing the mortality rate of appendiceal peritonitis in any clinic are the type of cases received, the accuracy of clinical appraisal, the policy of treatment and the technical quality of the treatment. If any of these essential factors are ignored, the

comparison must be fallacious and misleading. We are therefore less concerned with comparing our mortality statistics with those of others than with trying to find out what factors influenced them and how they may be improved.

During the three years occupied in personally analyzing the records of cases of appendiceal peritonitis admitted to the Massachusetts General Hospital between January 1, 1929, and January 1, 1940, we have also treated or supervised the treatment of all cases of so-called "ruptured appendix." The clinical phase of the study was of value not only in enabling us to investigate new technics but also in forcing us to be realistic in our analysis of the previous records. These records relate to house patients, some of whom were operated on by members of the visiting staff and some by the house staff. The records were uniformly good, although not every one contained all the items of information we sought.

PART I. FOUR HUNDRED AND FORTY-FOUR CASES OF APPENDICEAL PERITONITIS WITHOUT PALPABLE MASS

The patients served by the Massachusetts General Hospital are almost entirely white and mainly comprise city dwellers. Sixty-five per cent of the present group were males. The mortality rate among males was 14.2 per cent, in contrast with 19 per cent among females, perhaps because the presence of peritonitis offered a more difficult differential diagnosis in females and thus led to a relatively higher mortality. The age incidence and mortality by decades (Table 2) of these cases were very similar to those for appendicitis as a whole: the mortality was lowest among young adults, in whom the incidence was highest, and highest among patients at the extremes of life, in whom appendicitis is least common. It is noteworthy, however, that 18 per cent of the 444 patients were infants and children under ten years of age;

ment. Inherent diagnostic difficulties and the pernicious habit of administering cathartics to fretful children are undoubtedly responsible.

During this eleven-year period, there have necessarily been variations in the technical quality of

TABLE 3. Annual Distribution of Cases Over an Eleven-Year Period.

Year	No. of Cases	MOR- BUND OR VERY ILL PATIENTS ON ENTRY %	INC- DENCE OF IMMEDIATE APPEN- DICTOMY %	MOR- TALITY OF IMMEDIATE APPEN- DICTOMY %	MOR- TALITY OF ALL OTHER TREAT- MENT %	TOTAL MOR- TALITY %
1929	26	47	100	25	—	25
1930	28	21	93	23	50	25
1931	54	32	93	12	75	17
1932	54	30	96	15	50	25
1933	40	45	83	18	57	18
1934	34	29	82	14	33	14
1935	36	20	89	9	50	8
1936	77	27	92	4	50	26
1937	27	59	74	20	43	9
1938	35	26	80	4	29	9
1939	31	45	87	7	0	6
Total	444					
Averages		32.7	89.1	12.6	41.7	15.9

TABLE 2. Age Incidence and Mortality by Decades.

AGE	No. OF CASES	INCIDENCE %	No. OF DEATHS	MORTALITY %
Jr.				
1-9	79	18	16	20
10-19	154	35	18	11
20-29	69	15	9	13
30-39	35	8	5	14
40-49	43	10	7	16
50-59	33	8	6	18
60 or over	31	7	10	32
Totals	444		71	
Average				15.9

this suggests that an unfortunately large number of young children with appendicitis are being allowed to progress to the stage of actual peritonitis before being taken to the hospital for treat-

the treatment and the accuracy of clinical appraisal, as well as in the annual difference in the number and type of cases and progressive changes in the policy of management. No one of these factors alone was responsible for the different annual mortality rates (Table 3), although the types of cases appear to have made the greatest difference, and ironically enough, of all the possible variables this is the one over which we exercise the least control.

since it depends almost entirely on the diagnostic acumen of the medical attendant. That the policy of treatment was rather inflexible during this period is suggested by the consistently high proportion of patients subjected to immediate appendectomy—100 per cent in the highest year and 74 per cent in the lowest, with an average of 89 per cent. In the future, an increasingly flexible policy will be adopted, since it is shown that newer methods not only make appendectomy itself safer but also guarantee the surgeon greater freedom to choose the optimum time for doing it. But this widening scope of free choice, to be successful, implies the exercise of a high degree of clinical judgment and points directly to the importance of an accurate evaluation of preoperative clinical factors in terms of prognosis.

### PROGNOSTIC SIGNIFICANCE OF HISTORY

#### *Episode Suggestive of Acute Perforation*

At some definite time in their illness, one quarter of the 444 patients described a sudden episode that suggested acute perforation of the appendix, and the mortality (25 per cent) among these 115 patients was almost double that (13 per cent) of

ill give a history suggestive of acute perforation of more than six hours' duration, the symptom probably has no prognostic significance.

In the very ill group, the delay of even six hours (Table 4) between the acute perforation episode and operation resulted in a mortality rate (50 per cent) five times as great as that resulting from operation within six hours. This mortality rate certainly challenges the wisdom of routine appendectomy under such circumstances. On the other hand, we are not prepared to say that conservative treatment would have resulted better, since this group probably contains most of the cases in which spontaneous localization will never occur. We have not yet had enough experience with appendectomy combined with local chemotherapy to know how effective it will prove in this situation. We do know that in this group every case must be studied individually, and that operation should be elected only after all the significant factors have been weighed. Even then, a predetermined type of appendectomy should be avoided, and full advantage should be taken of whatever additional information is furnished by operative visualization to select the safest further procedure under the circumstances.

#### *Duration of Illness Before Operation*

The familiar phrase, "Too late for an early operation, and too early for a late operation," reflects the value that has always been attached to the time element as a guide for safe operation. In this series, the mortality rate more than doubled after the first day of the disease (Table 5) and did

TABLE 4 *Prognostic Significance of Time of Operation in Ill and Not Very Ill Patients with Acute Perforation*

DELAY FROM SYMPTOMS TO APPENDECTOMY	VERY ILL PATIENTS			NOT VERY ILL PATIENTS		
	NO OF CASES	NO OF DEATHS	MOR TALITY %	NO OF CASES	NO OF DEATHS	MOR TALITY %
0-5	11	1	9	14	1	7
6-8	14	7	50	14	0	0
9-11	5	2	40	0	0	0
12-17	12	4	33	19	2	11
18-23	7	5	70	2	1	50
24-72	8	5	63	9	0	0
Totals	57	24		58	4	
Averages			42			7

the 329 patients whose story suggested no definite hour of perforation.

Actually, the prognostic significance of such a story was confined to those patients who looked very ill on admission (Table 4). The mortality rate (42 per cent) was six times higher than that (7 per cent) of the patients who, with or without a history of acute perforation, did not look very ill. The story, the appearance of extreme illness and the high mortality were all presumably due to a relatively sudden gross contamination of the unprotected peritoneal cavity, either from an abrupt purging of protective adhesions or from a massive rupture of an insufficiently walled-off appendix. The patients who did not look very ill presumably did not have this pathologic picture, since so few (7 per cent) of them died. It must therefore be assumed that when patients who do not look very

TABLE 5 *Mortality and Morbidity According to Day of Disease on Which Appendectomy Was Done*

DAY OF DISEASE WHEN APPENDECTOMY DONE	NO OF PATIENTS	NO OF DEATHS	MOR TALITY %	INCIDENCE OF STOMY CONVA LESCENCE AMONG SURVIVORS	AVERAGE HOSPITAL STAY OF SUR VIVORS days
First	79	5	6	34	19
Second	158	23	15	36	20
Third	109	12	11	36	21
Fourth	29	7	24	34	21
Fifth	10	2	20	63	18
After fifth	11	1	9	60	25
Totals	396	50			
Averages			12.6	37	19.8

not decline until after the fifth day. It is of interest that the postoperative course of the survivors was little influenced by the day of operation, however, even when it fell within the most dangerous period, and this suggests that the day of the disease had much more significance for some patients than for others. The time element therefore served only to point out a group containing patients who would fail to survive appendectomy; it did not

identify the patients. This ultimate desideratum must depend on an appraisal of all the other significant factors in each case.

Chills

The preoperative occurrence of chills was described in the history of 41 patients, representing a minimal incidence of 9 per cent. These patients suffered a mortality rate of 22 per cent, as compared with a mortality of 16 per cent for the whole group of 444. The proportion of stormy convalescences and the average hospital stay of the 32 survivors did not differ from the average for the whole group. There were 4 recognized cases of pylephlebitis, 3 of which were fatal.

This experience may be summarized by the statement that about one tenth of the patients with appendiceal peritonitis without a palpable

nificant relation to the mortality rate than any other single preoperative factor. Reducing the classification to "very ill" and "not very ill," we have found the mortality associated with the former group (33.8 per cent) to have been almost five times higher than that associated with the latter (7.4 per cent), regardless of whether or not immediate appendectomy was carried out (Table 6).

Absent Peristalsis

Definite, complete absence of audible peristalsis in 53 cases was associated with a mortality rate (28 per cent) four times higher than that (7 per cent) of 115 cases in which the peristalsis was definitely present, and almost twice as high as the 16 per cent rate for 25 cases in which the presence of peristalsis was doubtful. As a single measure of

TABLE 6. Mortality in Cases, Variouslly Treated, According to Degree of Illness on Admission.

TREATMENT	TOTAL NO OF CASES	VERY ILL PATIENTS			NOT VERY ILL PATIENTS		
		NO OF CASES	NO OF DEATHS	MORTALITY %	NO. OF CASES	NO OF DEATHS	MORTALITY %
Immediate appendectomy	395	112	30	27	287	20	7
Deferred appendectomy	9	3	0		6	0	
Immediate incision and drainage	13	10	6		3	1	33
Deferred incision and drainage	16	13	6	46	3	0	
No operation	11	7	7		4	1	25
Totals	444	145	49		299	22	
Averages				33.8			7.4

mass gave a story of chills, that nine times out of ten it had no prognostic significance, but that the tenth time it meant a probably fatal pylephlebitis.

Previous Attacks

The well-recognized tendency of repeated attacks of appendicitis to increase in severity suggests that peritonitis following a series of attacks should result in a higher mortality than peritonitis complicating an initial attack. It is therefore of some interest that the mortality was about 2 per cent lower in a group of 110 patients who had had repeated attacks than in a similar group who developed peritonitis in their first attack. The difference, though small, suggests that the rapidity and extent of spread of peritonitis may be limited or delayed by the effects of the inflammatory reactions due to previous attacks.

PROGNOSTIC SIGNIFICANCE OF PHYSICAL EXAMINATION

Degree of Illness

The item "general appearance," which appears on the examination sheet in use at the Massachusetts General Hospital, is filled in by the admitting surgeon with a remark — such as "moribund," "very ill," "moderately ill" or "not ill" — that expresses his first impression of the patient's condition. This item has proved to have a more sig-

lethal degrees of peritonitis, it appeared to rank next in importance to the general appearance of the patient.

Abdominal Spasm

In 215 cases, spasm was described as diffuse or generalized, and the mortality was 21 per cent. This was twice as high as the 10 per cent mortality suffered by 199 patients with only local spasm, and over three times higher than that (6 per cent) of 16 patients who had no abdominal spasm at all. Thus, on the basis of 430 cases, the extent of spasm appeared to be the third most significant factor in the physical examinations.

Rectal Tenderness

Almost twice as many (21 per cent) of the 77 patients who did not have rectal tenderness died of the 277 patients who did (13 per cent). The rather surprising relation suggests that the direction in which the peritonitis spreads is perhaps of more significance than its actual extent, and such an explanation fits in with the well-recognized ability of the pelvic peritoneum to resist infection.

PROGNOSTIC SIGNIFICANCE OF LABORATORY DATA

Leukocyte-Pulse Index

That the original temperature, pulse and leukocyte count have more than a diagnostic significance

is generally appreciated, but just how and to what extent they may be used as an aid to prognosis and treatment is less well understood.

There is ample reason to believe that an abnormally rapid pulse in a patient with peritonitis is a measure of toxicity, whereas an accompanying leukocytosis reflects the degree to which the patient can mobilize his cellular elements to resist infection. (The significance of temperature variations is less clear, but it appears roughly to parallel that of the leukocyte count.) The relation between the amount of leukocytosis and the rapidity of the pulse might therefore be expected to represent the relative strength of the forces of destruction and of protection and hence to have a direct bearing on the prognosis of the case. In the absence of acute sepsis, such a concept would, of course, have no meaning.

We have attempted to express this relation by dividing the thousands of the leukocyte count into the pulse rate, to obtain a single number, which may be called the "leukocyte-pulse index." It might have been possible, by mathematical manipulations, to cancel the normal element from both components and thus obtain a truer expression of

succumbed; the leukocyte-pulse index averaged below 6 for the survivors and above 6 for the fatalities, and children had the same relation as adults but based on higher counts. From these averages, we have taken 6 to represent the critical point in mortality prognosis.

The mortality for patients with a leukocyte-pulse index below 6 was 6 per cent, but for those having an index above 6 it was 21 per cent, or more than three times as great (Table 7). This difference is large enough to exclude coincidence, so that a definite prognostic significance may be attached to it in cases of acute appendiceal peritonitis without mass formation.

#### Other Laboratory Data

Routine urine examinations were done, but we have not included them except to note how often blood cells appeared in the sediment as a possibly confusing diagnostic factor. Red cells were found in 19 cases and white cells in 70. We examined catheter specimens of female patients to be certain that the cells originated in the urinary tract.

Differential blood counts and other special procedures were omitted from this study, since there were too few for useful analysis. We believe that they should be done whenever the clinical diagnosis is in doubt.

TABLE 7. *Relative Prognostic Value of Various Clinical Factors as Determined by the Mortality Rate Associated with Each Factor, Based on 444 Cases with a Total Mortality of 15.9 Per Cent*

CLINICAL FACTOR	MORTALITY WITH FACTOR PRESENT	MORTALITY WITH FACTOR ABSENT
	%	%
Story of "acute perforation" in very ill patient	42	7
Patient very ill on admission	34	7
Peristalsis definitely absent	38	9
Wrong preoperative diagnosis	33	15
Age over sixty years	32	15
Peristalsis not definitely present	23	7
Leukocyte pulse index above 6	21	6
Story of "acute perforation"	25	13
Abdominal spasm diffuse	21	10
Operation not on first day of disease	18	7
Age below ten or above sixty years	24	13
Abdominal spasm present	16	6
Rectal tenderness absent	21	13
Story of preoperative chills	22	15
Age under ten years	20	15
Female sex	19	14
First attack of appendicitis	13	11

#### PROGNOSTIC SIGNIFICANCE OF DIAGNOSTIC ERRORS

As mentioned above, we have eliminated those cases in which the diagnosis of appendiceal peritonitis was proved to be wrong. Most of them were uncomplicated acute appendicitis without gross peritonitis and were treated by immediate appendectomy, and the patients did well, as would be expected in the early stages of the disease. So far as we could tell, no patient was allowed to rupture his appendix in the hospital because of the mistaken idea that it had already ruptured and should therefore be treated conservatively. The danger of falling into this error must be recalled, however, when the choice of deferring operation is under consideration.

The only diagnostic errors included in this study occurred in the cases that were actually appendiceal peritonitis but were mistaken for something else. There were 18, of which 6 were fatal, a mortality of 33 per cent, which is more than double that for the 426 correctly diagnosed cases. The mistaken preoperative diagnoses were perforated peptic ulcer in 5 cases (2 fatal), diagnosis in doubt in 4 cases (2 fatal), acute salpingitis in 3 cases (1 fatal), acute unruptured appendicitis in 2 cases, acute hepatitis in 1 fatal case, and acute cholecystitis, acute pancreatitis and ovarian carcinoma each in 1 case.

the significant relation, but we have refrained in the interests of simplicity. For example, with a leukocyte count of 20,000 and a pulse rate of 100, the index is 100 divided by 20, or 5.

In tabulating the average figures for living and dead patients, we have used the preoperative data of 335 patients subjected to immediate appendectomy, omitting the 27 patients over sixty years of age because they showed a rather different relation and yet were too few to permit an adequate investigation of this variation. The 292 patients who survived tended to have more leukocytosis in relation to their pulse-rate than the 43 who

It is apparent that these errors affected the mortality prognosis unfavorably only so far as the misdirected treatment of each patient was incompatible with recovery from acute appendiceal peritonitis.

#### SUMMARY OF PROGNOSTIC PREOPERATIVE FACTORS

Table 7 presents some of the factors that are familiarly thought of in terms of pathology but could be more directly used as guides for the selection of treatment if they were interpreted in terms of prognosis. An attempt has been made to arrange them in the order of their prognostic significance, the mortality rate of two groups of similarly treated patients being contrasted; one

moribund (Table 6) — reflects the nature of the policy then in force, and the mortality of 14 per cent seems remarkably low in view of the fact that one third of the patients were very ill at the time of operation. By contrast, the small group selected for expectant treatment was largely (two thirds) composed of very ill or moribund patients, and that this group should have suffered a 39 per cent mortality rate is not surprising.

Evidence of a gradual change of policy may be found in the annual figures (Table 3). The proportion of patients subjected to immediate appendectomy in the presence of peritonitis declined from 100 per cent in 1929 to 87 per cent in 1939, with a parallel decline in the mortality rate from

TABLE 8. *Mortality According to Choice of Treatment.*

TREATMENT	NO. OF CASES	INCIDENCE %	NO. OF DEATHS	MORTALITY %
Immediate operation	408	92	57	14
Immediate appendectomy	395	89.1	50	12.6
Immediate incision and drainage alone	13	2.7	7	54
Expectant treatment	36	8	14	39
Deferred incision and drainage alone	16	3.6	6	38
Deferred appendectomy	9	2.0	0	0
No operation	11	2.6	8	73
Totals	444		71	
Average				15.9

group was characterized by the presence of some factor, and the other group by its absence. It is realized that no such correlation can be taken too literally because the contrasted groups could not be identical in every particular save the one under consideration.

We believe that when several of the most unfavorable factors are combined in one case, the patient must be recognized as an extremely bad risk, and that particular care must be taken in selecting the safest treatment.

#### INFLUENCE OF TREATMENT ON MORTALITY RATE

##### *Choice of Treatment*

At the Massachusetts General Hospital during most of the period covered by this study, the policy favored immediate operation at any stage of the disease, provided only that the patient appeared strong enough to stand the operation. More recently, the wisdom of operation in the presence of gross peritonitis has been increasingly questioned, particularly since the newer methods of controlling ileus, distention, fluid imbalance and infection have increased the efficacy of expectant treatment.

The fact that immediate operation was chosen in 91.9 per cent of our cases (Table 8) — even for 84 per cent of the patients who were very ill or

25 to 6 per cent. We believe that this shift in policy and improvement in the mortality figure was partly due to an increasing recognition of the value of accurate individualization.

##### *Technical Factors*

It is apparent that the different degrees of technical skill of the surgeons who operated on the patients in this series must have had a significant effect on the mortality rate, but one that would be extremely difficult to calculate or to control. It has been profitable to examine certain technical factors, however.

*Type of incision.* For purposes of comparison we have divided incisions into two main types: lateral and medial. The former refers to the relatively small gridiron incisions, as described by McBurney and Rockey, characterized by a minimal exposure of small bowel. The medial type includes midline, paramedian, rectus-splitting and rectus-retracting incisions, all characterized by greater exposure and manipulation of viscera, especially small bowel.

Appendectomy was seldom done through a McBurney type incision, and its use in case without a mass appears to have made no difference in the mortality rate. The survivor of appendectomy had an identical incidence of stormy convalescence (36 per cent) and average

an identical number of hospital days (twenty), regardless of the type of incision used.

The choice of incision appeared to make a great difference in the 26 cases of incision and drainage without appendectomy: the mortality was almost three times higher when a median type of incision was used (Table 9). Again, the survivors had an identical incidence of stormy convalescence (40 per cent), regardless of the type of incision, which is perhaps only another way of saying that the patients did or did not get fatal general peritonitis as a result of surgical manipulations.

We believe that trauma to peritoneal surfaces with gauze packs, breaking down of protective adhesions and contamination of uninfected areas

of the others depended largely on the current popularity of one or another type.

Obviously, the correct choice of the anesthetic for every case is important, and if in every case the technic of its administration could be perfect, the correct choice would be solely a matter of correctly evaluating each patient. But faulty technic, resulting in an adequate degree of relaxation for the gentle, careful, safe sort of surgery that is essential in appendiceal peritonitis, may make any choice wrong. The correct choice must therefore depend partly on the quality of the available anesthesiologist, partly on the nature of the proposed operation, partly on the technical capabilities of the surgeon, and partly on the patient's physical and

TABLE 9. *Type of Incision and Associated Mortality.*

OPERATION	MEDIAL TYPE INCISION			LATERAL TYPE INCISION		
	NO OF CASES	NO OF DEATHS	MORTALITY %	NO OF CASES	NO OF DEATHS	MORTALITY %
Appendectomy, immediate	360	45	13	32	4	13
Appendectomy, deferred	5	0	0	3	0	0
Incision and drainage alone	17	10	59	9	2	22
Totals	382	55		44	6	
Averages			14.4			13.6

increase the mortality rate regardless of the incision through which such offenses are committed. They were absolutely inexcusable in the performance of simple drainage, in which adequate exposure was not a consideration. In appendectomy, on the other hand, the demands of adequate exposure and avoidance of fatal trauma had to be reconciled, and the care and skill of the surgeon were apparently of greater consequence than the type of incision.

The medial type of incision is frequently advocated for females for convenience in reaching the pelvic organs, should they prove to be the true source of the symptoms. There is no objection to this in the absence of peritonitis, but it may result badly when gross appendiceal peritonitis is present. When the presence of peritonitis is in doubt, two incisions are safer than one disastrously wrong one.

*Anesthetic.* No deaths could be definitely attributed to the anesthetic, but poor choice and poor administration undoubtedly contributed to some of them. Ether (287 cases), spinal (115 cases) and local (28 cases) anesthetics were most frequently chosen. How much the mortality associated with each type relates to the anesthetic and how much it reflects the sort of cases in which each was used cannot be determined. The specific reasons for choosing a spinal anesthetic in 23 cases and a local in 28 cases were recorded, but the choice in most

mental condition. We are convinced that these considerations fundamentally influence the mortality rate, but unfortunately they cannot be expressed in terms of statistics.

*Length of operation.* The time from the skin incision to the application of the dressing was accurately recorded in 392 appendectomies. The 392 operations averaged forty-nine minutes and resulted in a mortality of 12.6 per cent.

As might be expected, the mortality was higher among very ill patients (26 per cent), even though their operations averaged only about five sixths as long as those of not very ill patients. Comparing the average length of operations that resulted in death and in recovery, it was seen that among good-risk patients long operations were associated with death and shorter operations with recovery, whereas among very ill patients the shorter operations were followed by death and the longer ones by recovery. It is thus clear that there is no simple relation between length of operation and mortality. A comparison of the actual mortality rates for each length of operation shows that the shortest operations did not have the lowest mortality rates among either the very ill or the not very ill patients. In both groups, the lowest mortality was for operations lasting between fifty and sixty minutes, and after one hour the mortality rate began to rise (Table 10).

We may safely assume that what determined



the length of these operations was how difficult the removal of each particular appendix proved for the particular surgeon, in addition, of course, to his own estimate of the need for haste. When the combination resulted in a degree of damage from which recovery was impossible, the patient died. Viewed in this light, our figures mean that speed is not in itself desirable, that avoidance of trauma is essential, and that if an appendix cannot be removed without undue trauma in one hour it should not be removed by that surgeon at that operation.

The length of 83 appendectomies in children under eleven was thirty-six minutes, and the mortality was 15 per cent. Possibly, safe appendectomy

out through a stab wound rather than through the main incision. Intestinal obstruction developed in only 8 (2 per cent) of the 415 drained cases, and was fatal in only 1 case (0.2 per cent).

In 18 cases, the abdomen was closed without drainage. Two of these patients were very ill, and 16 were not very ill, at the time of operation. All 18 recovered. One developed intestinal obstruction, which required operation on the seventh day after appendectomy. Three others developed residual abscess requiring drainage. Five had stormy, prolonged convalescence, and the remaining 9 did well.

On the basis of this experience, we must conclude that properly placed cigarette drains do little c

TABLE 10. Mortality Rate for Each Length of Operation According to Degree of Illness in Cases of Immediate Appendectomy.

LENGTH OF OPERATION <i>min</i>	VERY ILL PATIENTS			NOT VERY ILL PATIENTS			ALL PATIENTS		
	NO OF CASES	NO OF DEATHS	MOR- TALITY %	NO OF CASES	NO OF DEATHS	MOR- TALITY %	NO OF CASES	NO OF DEATHS	MOR- TALITY %
20 or less	5	2	40	6	1	17	11	3	27
21-30	25	9	36	40	3	8	65	12	19
31-40	28	7	25	62	3	5	90	10	11
41-50	20	6	30	58	3	5	78	9	12
51-60	23	3	13	60	3	5	83	6	7
Over 60	10	2	20	55	8	15	65	10	15
Totals	111	29		281	21		392	50	
Averages			26			7.5			12.7

can be done more rapidly in children than in adults, but in the presence of peritonitis children tolerated rapid (and therefore perhaps rough) appendectomies no better than adults.

*Use of drains.* The time has passed when the surgeon at operation can fall back on some simple rule of thumb such as "When in doubt, drain" or "When in doubt, do not drain" and be satisfied that he has done the best thing for the patient. In view of the controversial opinions in the literature on the theoretical value of drainage, he cannot be blamed if he finds himself in doubt most of the time. With so many conflicting views advanced, there may be some practical value in noting the actual effects that could be attributed to the use of drains in the present cases.

Drains were used in the vast majority (96 per cent) of the 433 operative cases. Pus was removed by the suction tip, and two drains were placed most frequently (258 cases), one in the pelvis and one lateral to the cecum. Less frequently (128 cases), only one drain was used, either lateral to the cecum or in the pelvis. Three drains were used in 20 cases, and four drains in 9 cases.

An attempt was always made to avoid having any drain in contact with the small intestine or appendix stump. For this reason, it was thought desirable in 55 cases to bring the drain or drains

no harm, and that we have no evidence that would justify omitting them in cases of gross appendiceal peritonitis merely as a matter of policy.

*Other factors.* In recent years, blood transfusions have been given with greater frequency. In all, 51 of the 444 patients were transfused, each of these patients averaging two transfusions. Twenty-two patients died, and 29 recovered. These were obviously the sickest patients.

Chemotherapy was used successfully in 4 of the more recent cases covered by this report. Although it is now being used with increasing frequency, we have not had sufficient cases for useful analysis.

Smears and cultures may also assume greater importance as aids to treatment and prognosis, but since their full value was not appreciated during the earlier years covered by this study and since the laboratory methods have been changing and improving, we are not in a position to include this very interesting aspect of treatment.

There can be no question that part of the recent improvement shown by our own mortality figures and by those of others is due to improved methods of postoperative care based on more efficient therapeutic apparatus and better understanding of applied biologic chemistry. These factors, however, do not lend themselves to the statistical method of analysis, and we have therefore not attempted to

evaluate them as we have certain other technical factors concerned with the mortality rate.

### COMPLICATIONS

Residual abscesses following appendectomy (5 undrained, 35 drained) were encountered in 40 cases, with 4 deaths and an average of thirty-three hospital days for the survivors. Spontaneous resolution of the abscess took place in 20 cases. In the other 20, abdominal incision and drainage was necessary in 16, rectal puncture in 4. Nonfatal pneumonia was seen in 4 cases, and pneumonia was present in 8 cases of fatal peritonitis. Pulmonary infarcts were recognized in 2 cases, the patients averaging twenty-seven hospital days. Pulmonary collapse in 10 cases did not increase the length of hospitalization. There seemed to be no correlation between these pulmonary complications and the type of anesthesia.

There were 24 cases of major wound sepsis, 1 of wound dehiscence, and 1 of hemorrhage from the wound, all in drained cases, resulting in an average hospital stay of twenty-six days. Fecal fistula developed in 3 cases, with an average hospitalization of forty-four days, and all closed spontaneously. Two incisional hernias were noted, both following drained rectus-retracting incisions.

Nine cases of intestinal obstruction developed; 1 was fatal, and the other 8 resulted in an average hospital stay of thirty-eight days. Six of these patients had ileostomy done to relieve serious obstruction, since the Miller-Abbott tube was not then available.

Phlebitis lengthened the hospital time to twenty-seven days in 2 cases.

There was 1 case each of nonfatal pylephlebitis, urinary fistula, empyema, herpes zoster and pulmonary embolism, the hospital stays varying from one hundred and seventeen to seventeen days but averaging well above the nineteen-day period that was the average for the whole group.

### CAUSES OF DEATH

Of the 71 deaths, 49, or almost 70 per cent, were caused by general peritonitis, with or without such concomitant complications as pneumonia in 8 cases, intestinal obstruction in 3, septicemia in 1 and massive wound sepsis in 1. Six deaths were caused by pneumonia, with concomitant diabetes in 1 case and wound sepsis in 1. Three were caused by pylephlebitis, and 3 by pulmonary embolism. Sepsis, subphrenic abscess, gas gangrene, uremia, acute nephritis, right heart dilatation, myocardial failure and acute respiratory failure each caused death in 1 case; there were 2 undetermined causes, 1 of sudden death on the operating table and 1 of epileptiform convulsions six hours after operation, no autopsy being performed.

### PREVENTABILITY OF DEATHS

We have studied the records of the fatal cases to see if any of the 71 patients could have been saved by different management in the hospital. This is not easy to ascertain, since a number of elements, some of them unknown and indeterminate, combined to produce each death. We have, however, tried to pick out the cases in which some error that is known to be frequently fatal may have been made.

### Errors in Diagnosis

Two patients were explored through an upper abdominal incision for perforated duodenal ulcer a few hours after onset of symptoms, and both died of general peritonitis caused presumably by manual dissemination of pus from a ruptured appendix. This disaster would have been averted if the appendix had first been explored through a small incision in the right lower quadrant.

A nineteen-year-old girl at autopsy showed co-existent chronic salpingitis and ruptured appendix, with general peritonitis. She had entered the hospital on the first day of her acute symptoms, and had been treated conservatively for pelvic inflammation.

One woman entered the hospital in premature labor with atypical pain, died without operation, and at autopsy showed a ruptured appendix, with general peritonitis.

A child was studied for eleven days on our children's medical service, died without a diagnosis, and was found at autopsy to have a ruptured appendix and general peritonitis.

These were undoubtedly all difficult diagnostic problems, and similar ones are constantly being seen. Since appendicitis is by far the commonest abdominal emergency, we believe gentle exploration through a small McBurney incision to be justifiable whenever the presence of a ruptured appendix cannot be excluded and the contemplated treatment is incompatible with recovery from appendiceal peritonitis. We have frequently attempted to aspirate the peritoneal cavity in doubtful cases, with no ill effects so far, but a negative result is of no diagnostic significance, and the procedure cannot be regarded as free of risk.

### Wrong Choice of Treatment

Eleven of the appendectomies that were done between the third and the seventh day of the disease were fatal, the patients dying of general peritonitis. We cannot say that this was a wrong choice of treatment in these particular cases, but we can point out again that this is the phase of the disease in which appendectomy carries the highest mortality, when localization is trying to

take place, and when trauma to the peritoneal cavity is likeliest to be harmful. We are not convinced, however, that this dangerous period can be recognized by the day alone. All the data that reflect how well or how badly the patient is handling his infection must enter into the decision, as must the surgeon's personal ability to do a nontraumatic operation. Certainly, no oversimplified rule can be blindly followed as a guide to treatment. We believe that some of these 11 fatalities could have been prevented by a choice of treatment better fitted to the clinical indications.

### *Prolonged Surgery*

Five deaths followed appendectomies lasting from seventy to one hundred minutes. Only 1 of the patients was very ill before operation, yet all 5 died of either peritonitis or pneumonia within five days. We question the judgment of persisting beyond one hour with a difficult appendectomy in the presence of peritonitis. The temptation is all too great, especially among the younger surgeons, to allow personal considerations of pride to obscure the main issue of the patient's welfare, once appendectomy has been started. Some of these deaths might have been avoided had the surgeon made a gentle investigation, satisfied himself that appendectomy would be technically difficult and time-consuming, and then elected the lesser risk of draining the region of the appendix and ochsnerizing the patient until a safer time.

### *Errors in Technic*

Six patients who were not very ill before operation nevertheless died promptly of general peritonitis following operations that were neither unduly prolonged nor unwisely timed. The presumption is that rough handling, unnecessary exposure of intestines, unjustifiable packing of gauze into the abdomen and other technical crudities resulted in breaking down delicate protective barriers, with resultant wide dissemination of sepsis in the peritoneal cavity. To whatever extent these presumptions are true must the above six deaths be considered avoidable deaths.

### *Unavoidable Deaths*

Fourteen deaths apparently could not have been prevented. Ten patients were moribund on admission and failed to respond to Ochsner treatment reinforced by transfusions, Wangensteen drainage and other well-chosen efforts. Four other patients died during convalescence from successful operations, 3 of pulmonary embolism and 1 of acute nephritis.

Nineteen deaths were probably unavoidable, although not so clearly so as the above. This group

comprised deaths from pneumonia, pylephlebitis, gas gangrene, septicemia, epileptiform convulsions, acute respiratory failure, acute cardiac failure and peritonitis.

The remaining 11 deaths may or may not have been preventable, the circumstances admitting no presumption either way.

In conclusion, it should be emphasized that all 71 deaths were avoidable in the sense that earlier diagnosis and treatment of the 444 cases of acute appendicitis would have obviated the dangerous and difficult problems of peritonitis and its complications.

## SUMMARY AND CONCLUSIONS

The use of a clinical in place of a pathological basis of classification in a statistical review of 444 cases of appendiceal peritonitis without palpable mass formation has furnished guides for more accurate appraisal and hence more satisfactory individualization of treatment in such cases.

The great majority of deaths are due to progressive generalized peritonitis. The ability to recognize in advance the cases in which localization will or will not take place and to select the safest time for operation in each case, together with good preoperative and postoperative care and a minimum of trauma to the peritoneum, will determine the success of treatment.

The following conclusions seem justifiable:

Patients who look ill on admission and are operated on more than six hours after an incident interpreted as an acute perforation suffer the highest mortality (50 per cent).

A general appearance of being very ill is the most unfavorable prognostic sign, and absence of audible peristalsis is next in importance.

A pulse rate too rapid for the leukocyte count that accompanies it (leukocyte-pulse index over 6) is the most unfavorable prognostic laboratory observation.

The fourth and fifth days of the disease are the most dangerous for appendectomy (22 per cent mortality), the first day is the least (6 per cent). After the fifth day the mortality diminishes to about 9 per cent.

For incision and drainage alone, the McBurney type of incision is more than twice as safe as a medial type of incision. For appendectomy, the type of incision is of less consequence than the amount of trauma done through it.

About half the residual abscesses following appendectomy regress spontaneously.

- Appendectomy lasting between fifty and sixty minutes results in about half the mortality rate of either longer or shorter operations

The proper use of cigarette drains is satisfactory and safe.

When the diagnosis is in doubt and the con

templated treatment is incompatible with recovery from acute appendiceal peritonitis, a fatality may sometimes be avoided by a preliminary gentle exploration through a small McBurney incision.

*(To be concluded)*

## BOSTON MEDICAL LIBRARY

### REPORT OF THE PRESIDENT FOR THE YEAR 1941\*

ALTHOUGH there appears to be no definite provision in Article XVI of the by laws, which prescribes the order of business at the annual meeting, for a communication from the president, perhaps under "Incidental Business" it may be appropriate for him to report on the "State of the Library" with a view especially to telling of the needs and planning for its greater usefulness and prosperity in the future

He who attempts to appraise an institution without first exploring its history is likely to fail truly to understand its character and significance, and I should therefore like to recommend to all of you as "required reading" the fascinating account by our late Librarian, Dr. Farlow, of the efforts, during one hundred and fifty years, of the physicians of Boston to secure the advantages of a medical library. With the passion of our forebears for education, it is likely that, quite unknown to us, groups were formed to share the half dozen medical and scientific journals, and the few medical volumes brought to this country from abroad. The Medical Improvement Society, organized in 1803 by men many of whose surnames may be found on our roster of today, gathered together books that they held under a statute of 1798 as the Second Social or Boston Medical Library, these volumes were housed at Dr. John Fleet's, and a little later at the apothecary shop of Amos Smith, 39 Marlboro Street (now near the corner of Washington and Milk streets). Among the moving spirits, as anyone would predict, were young John C. Warren, treasurer and later librarian, and his friend James Jackson. A list of the books at this time shows twenty-nine titles. Young Dr. Warren was giving a course in anatomy in rooms over White's apothecary shop at 49 Marlboro Street (Washington Street, near the corner of Franklin), and since he was librarian of the little library, it was natural that the books should be moved there from Smith's apothecary shop. At about this time, 1810, the Harvard Medical School, consisting of the persons

of Dr. John Warren, Sr., Dr. Benjamin Waterhouse and Dr. Dexter and their lecture notes, was transferred there from Cambridge. Moreover, Dr. Thomas I. Parker, who had become librarian of the little collection, had his private office at the same address. Later, in 1819, after the medical school had moved to Mason Street, the Boston Medical Library accompanied it to that building, so that it was housed and doubtless closely identified with the school at these two locations, and probably in the latter building was actually united with whatever books had been collected by the Massachusetts Medical College, as the future Harvard Medical School was then called. But the faculty, for reasons now unknown, apparently allowed the alliance to lapse, and in 1826 the accumulated two thousand volumes of the Boston Medical Library, appraised at \$4500, were conveyed to the Boston Athenaeum, which was absorbing various circulating libraries of Boston to enrich its collections, and the thirty-one physicians who, of the seventy-one in Boston, were members of the Library became proprietors of the Athenaeum. Thus, after an adventurous existence of twenty three years, the Boston Medical Library lost its corporate identity, and even its name lapsed as designating a group of books on medical subjects in the Athenaeum. At least two other futile attempts—one by the Observation Society in 1848 and another by the Suffolk District Medical Society—to start a library indicate the need felt by Boston physicians for such an institution.

This was the situation when Dr. James R. Chadwick, thirty years of age, recently returned from Europe, became obsessed with the idea that some at least of the advantages of study abroad could be secured for the doctors of Boston by the establishment of a working and reference library. A preliminary meeting was held on December 21, 1874, and a second meeting one week later, at the office of Dr. Henry I. Bowditch. Final organization was accomplished on August 20, 1875. With the names of those present as a text might be written the history of medicine

\*Read at the annual meeting of the Boston Medical Library, March 3, 1942.

in Boston: Bowditch — anti-slavery agitator, co-discoverer with Dr. Morrill Wyman of paracentesis of the thorax, one-time Jackson Professor of Clinical Medicine, founder of the Society for Medical Improvement — was the first chairman of the first board of health established by any state in the Union; Oliver Wendell Holmes was Parkman Professor of Anatomy and already a great figure among New England literati; Samuel A. Green had a splendid Civil War record and was a historian, a man of letters and later to be mayor of Boston; and Francis Minot was Hersey Professor of Theory and Practice. Associated with these elder statesmen of medicine was a group of younger men of from thirty to forty years of age, including Thomas Dwight, F. I. Knight, R. T. Edes, Henry P. Bowditch, Clarence J. Blake, Charles P. Putnam, C. E. Stedman, William L. Richardson, Edward H. Wigglesworth, Reginald H. Fitz, Francis W. Draper, E. J. Forster, James B. Ayer, A. Lawrence Mason and Oliver Wadsworth — young, enthusiastic, almost to a man destined for high teaching positions, often of professorial rank, in the Harvard Medical School. Holmes was chosen president, Wadsworth secretary, Mason treasurer, and Chadwick librarian.

In October, 1875, two rooms in the basement of 5 Hamilton Place, opposite the Park Street Church, were secured and fitted with two tables, thirteen chairs and some bookshelves. Chadwick's zeal secured the exchanges of the *Boston Medical and Surgical Journal* and the collection of the Society of Medical Observation; the libraries of Dr. George Hayward, clinical professor of surgery, Edward H. Clarke, professor of materia medica, and George Cheyne Shattuck, founder of the Shattuck Professorship of Pathological Anatomy, poured in and were piled on the floor. Soon, there was scarcely room for readers, and the invincible enthusiasts begged and subscribed more money, placed a mortgage and purchased a little house at 19 Boylston Place, once the home of the philanthropist, Dr. Samuel Gridley Howe and his wife Julia Ward Howe. At the dedication ceremonies on December 3, 1876, addresses were made by the president, Dr. Holmes, Dr. John Shaw Billings, librarian of the National Medical Library in Washington, Professor Justin Winsor, librarian of Harvard College, Dr. George H. Lyman, president of the Massachusetts Medical Society, Dr. Calvin Ellis, dean of the Harvard Medical School, Charles W. Eliot, president of Harvard College, and Dr. Henry I. Bowditch. These names are set down as the best indication of the importance ascribed to the occasion by the intellectual leaders of the community.

In the new location, more accessions poured in. From the Massachusetts Medical Society came fif-

teen hundred items; from the library of Dr. J. Orne Green, seven hundred volumes; from the Harvard Medical School, its collection of periodicals and many books, in exchange for duplicate textbooks; and from Dr. Calvin Ellis, late professor of clinical medicine and dean of the Harvard Medical School, his valuable library. By 1886, ten years after removal to the new location, the building was becoming overcrowded. Drs. F. C. Shattuck and Charles R. Putnam established a directory of nurses, which found office space in the library, for which it paid a welcome rental. The councilors of the Massachusetts Medical Society began to meet in the reading room. A possible solution was seen in the proposed inclusion of the library in the new building of the Harvard Medical School at the corner of Boylston and Exeter streets, but the project was not deemed feasible. When Holmes, three years before his death, presented nearly a thousand volumes and caused to be built the bookcases to house them, when the Boston Athenaeum gave its entire medical collection, including the two thousand volumes formerly belonging to the Second Social or Boston Medical Library, which had reposed on its shelves for seventy years, and when the libraries of Edward Wigglesworth, Henry J. Bigelow, Conrad Wesselhoeft and many volumes from the Warren family were added, the problems of overcrowding and of financial support became as acute as ever. How these were solved for a time by generous gifts and bequests and by the building in 1900 of our present splendid house on the Fenway, how we have been enriched by the William Norton Bullard and by the Hyams collections of incunabula and manuscripts, and how portraits, engravings, letters, medals and medical memorabilia have been entrusted to us for posterity constitute a story too long to tell here. Our plant cost half a million dollars; our books and treasures are carried at an equal sum, but are, of course, actually irreplaceable. We stand fourth among the medical libraries in America.

Our past, at least is secure, but what of the future? It occasions your trustees grave anxiety. The Library looks well nourished and presents — with some reservations — an outward appearance of health, but its intimate advisers know that it is anemic and that its vital organs are suffering from financial anoxia. It is operated on an annual income of less than \$32,000 of which less than half is income from an endowment that has suffered serious capital depletion, less than a third is from dues, and the rest is from rental of space and from gifts and miscellaneous sources. We have never been able to complete the stacks, periodical room and other facilities for which our new addition — built with funds raised by the campaign of 1929-1930 — was designed. Thousands of books are

piled in the basement awaiting shelving or other disposition, hundreds of volumes of periodicals are unbound and wrapped for preservation in paper or temporary covers. Thousands of bindings should be renewed. Our salaried staff—but five in number—are numerically inadequate, devoted though they are. Our director, completing his fiftieth year of continuous service, must be supposed to be mortal,—ageless though he seems,—and his accumulated experience and knowledge should be communicated to a young associate. Our fellows—now some eight hundred in number, have diminished by one hundred during the past year. Most of them have shown a loyal spirit of support, like the late George Craigin, who—although long retired—rounded out fifty years of membership, finally terminated by his recent decease. But surely there must be twice as many physicians in Greater Boston and New England who would offer support did they realize our need. Perhaps our very liberality in opening our doors and reading rooms to any reputable citizen, whether or not a physician, has lightened our purse. Furthermore, our marrow has been stimulated recently by radical therapy, which—however optimistic we may be—must be considered fortuitous and not dependable so far as the future is concerned. The bequest of \$25,000 by Dr. Holmes's daughter, subject to a life interest of her brother, Justice Holmes, became available recently and was devoted to the payment of debts and to needed renovation of our building; half the \$10,000 bequest of Dr. John W. Farlow, our second librarian, was spent on repairs; two thirds of a similar sum, a gift from the family of our first secretary, Dr. Oliver F. Wadsworth, and of his son Richard—a later treasurer—was used in renovation and furnishings, and most unpredictable of all, the WPA carried out a splendid project of sorting, classifying, cleaning, cataloguing, boxing and shelving that represented a money value of \$75,000. Idle hands now find other occupation.

Perhaps, in these paragraphs, you have gained a true impression of our library in its earlier years, as an institution sorely needed by the closely knit medical profession of its time, supported by the mental and actual manual labor and by the purses of most of the physicians of Boston who amounted to anything, closely associated with the Harvard Medical School and its graduates because there were no others, and subject to no rivals as a source of medical literature. Great changes that have since occurred pose new problems. Fortunately for Boston and New England and the world at large, the medical schools of Boston University and of Tufts College have been born and have

prospered, and each takes pride in a working library of its own. That of the Harvard Medical School—necessarily with powerful support—has grown by leaps and bounds. Each hospital maintains its library for the use of staff and interns and nurses. Moreover, the individual physician receives from two to ten or more periodicals,—depending on the societies to which he belongs and his special interests,—which, with their abstracts, supply him with all the current medical information he can absorb. There is danger of—indeed there exists—duplication of effort, which is wasteful, and division of support, which is unfortunate. Let it be emphasized, however, that among the various medical libraries exists cordial co-operation: several hold “professional membership” in our library and constantly make use of the privilege of supplementing their books of reference.

Confronted by these facts and tendencies as they have developed over the years, your trustees have given *serious consideration to various proposals*, involving usually some form of alliance or amalgamation, with increased opportunity for service. Sixteen years ago, a plan for an academy, with our library as its nucleus, advanced to a point where a charter was obtained, and tentative plans were drawn. Of this project and the reasons for its failure, your president has no personal knowledge. Once more, however, the subject is ripe for review, especially because there is available an illuminating survey of the medical libraries of Boston, with recommendations for the future, from an authoritative source.

Through the good offices of the director of the Harvard University Library, the Carnegie Corporation financed the commission of Mr. Thomas P. Fleming, medical librarian of the College of Physicians and Surgeons of Columbia University, to examine all our medical libraries, to confer with a committee and make a report with recommendations. The work was done during the summer and autumn of 1941. Mr. Fleming made an elaborate factual survey of eleven libraries, with their many subordinate units, and the committee made a report that has been appropriately distributed. The findings that especially concern us are as follows:

That the Boston Medical Library is centrally located and has sufficient storage space for many years to come; . . . that because of lack of funds it is understaffed and does not furnish the type of service, in regard to either quantity or quality, that is to be expected; . . . that its future—particularly in view of present-day attempts to eliminate decentralization and duplication—hinges about its development as a *reference library*, not only for the benefit of Boston and its immediate vicinity but also for the rest of Massachusetts and other New England states.

The recommendations made by the committee include:

That the staff of the Boston Medical Library be increased, to provide adequate and efficient service; . . . that all working libraries co-operate with it . . . and use it to best advantage as their reference library; . . . that either (a) a very substantial sum of money be obtained to erect a new building, to be known as the New England Academy of Medicine, which would house not only the Academy but also the Boston Medical Library and the Massachusetts Medical Society, including the *New England Journal of Medicine*, or (b) a substantial sum of money be obtained . . . to make the necessary alterations in the Boston Medical Library to provide attractive modern facilities and adequate stacks, and to cover in part, through increased income, the additional expense incurred by increases in its staff; . . . that the financial support of the Boston Medical Library by the working libraries be increased, in view of the improvement in service rendered to them

and of the opportunity to cut down on their annual expenditures.

Already, plans are made by a group of men, among whom representatives of our library are conspicuous, to explore every possibility and to devise and later attempt to execute a comprehensive, broadly conceived plan for the future. As a Nation, we are literally in a death struggle with an implacable, relentless and powerful foe whose purpose is to enslave us, and it is quite likely that many of us may say that this is no time to bother about matters that seem to have no relation to the struggle we are making to win the war. Surely on further thought, however, every man of us will realize that this is the time of all others when we must guard and hold fast that which is good and has been amply proved to be a source of strength and inspiration.

DAVID CHIEVER, *President*

## REPORT OF THE LIBRARIAN FOR THE YEAR 1941\*

THE year 1941 saw the Boston Medical Library pass from a period of national emergency to one of war. Libraries pass through wars, except when destroyed, as some of our sister institutions in Great Britain and elsewhere were, less affected than many of our national foundations. Our stock in trade, books, still retain their influence even if uprooted and transferred to other quarters. Certain of our most valuable possessions have been moved to places of comparative safety, where they are still available but not so prominently displayed. The very moving has been helpful in recounting our treasures and will probably lead to a recataloguing of our most valuable books. Our incunabula in the Bullard Collection were last catalogued in 1929. Since that date, this one group of books has tripled in size, and to them have been added others in the Hyams Collection. Our manuscripts have also grown in number, and it now seems fitting to print a new list of all the manuscripts and books in the library known to have been issued before 1500. Such a volume is indeed contemplated. Fortunately, too, this year will see the completion of fifty years of service to the Boston Medical Library by Mr. James F. Ballard, whose knowledge of these books is outstanding. To him must fall the work of compiling the catalogue, but to the fellows and friends of the Library comes the opportunity to honor a man devoted to our interests.

The war has brought, as might be expected, certain changes in our library life. All foreign periodicals, except those coming from Great Brit-

ain and Russia, are now frozen in their respective countries. In some instances, before the mails closed down entirely, arrangements were made to hold periodicals for future delivery. Except for a few issues, presumably lost in transit, English periodicals are received regularly. During the year, large shipments of medical magazines were received from Russia by exchange for duplicate American journals. In view of the lack of foreign journals, the usual gifts for their purchase from the local medical societies were not solicited during the year. However, gifts for periodicals were generously donated by the New England Pediatric Society and the Greater Boston Medical Society.

The national emergency also closed, on June 30, our two projects of the Works Progress Administration. Much, however, had been accomplished, particularly in sorting and classifying our theses and in putting our catalogue in shape. The *Union Catalogue*, fortunately, was practically completed, except for typing of the cards. This additional portion, essential to make the catalogue useful, awaits only additional funds. Although the projects have stopped, we can regard the work done as a definite contribution of considerable value to the Library. One of the aspects, moreover, is being carried on to completion. The Boston Medical Library catalogue cards are being copied, as agreed, for the library of the Harvard Medical School. This is about half finished. The proposed binding project, also to be under the Works Progress Administration, was never begun. Certain binding apparatus, purchased in anticipation

\*Presented at the annual meeting of the Boston Medical Library on March 3, 1942.

of the project, is a valuable accession to the Library. It is always salable, but will be held for the time being.

The war, also, has caused a change in our hours of opening and closing the Library, owing to a curtailment of oil used for heating. The hours were greatly restricted at one time, along with those of our tenants and our neighbor, who buys heat from us. Later in the year, we were able to lessen the restriction on hours, and at the present time we are open for a normal period.

Attendance and circulation have been maintained at approximately the same level as in 1940. The circulation, as was noted last year, is 25 per cent greater than it was in 1939. Ten thousand more books, pamphlets and bound or current journals are thus handled each year by our small staff, a heavy drain on their energies and good nature. In addition, our interlibrary loans have jumped from 219 items to sixty-two libraries in 1939 to 633 items to one hundred and twenty libraries in 1941. The assembling, the packaging, the arrangements for fees and their collection, the answering of correspondence and the supervision of these loans are a not inconsiderable added burden on the reference librarian. If the call for books, moreover, both by our readers and by loan, is kept up as the years go by, we shall be faced with an even more acute problem than we have known about for years. Our staff is too small to give adequate service.

In 1941, we added 2432 volumes to our store of books, somewhat less than in previous years. This is largely due to the decrease in volumes of periodical literature received owing to war conditions: only 582 volumes in 1941 as compared with 1995 volumes in 1939. The number of books acquired has actually increased from 1432 to 1824. Thus, our library grows in both stature and usefulness each year, but at the same time the labors of our staff are increasing. If we seem a little "short," we are just trying to put quarts into pints, or as Osler would say, we are driven from Dan to Beersheba.

A number of papers have been published by the staff, directly related to the Library. The director issued his annual report, "The Medical Books of 1940," in the *Bulletin of the Medical Library Association* for June. The Librarian's "Report for 1940" was printed in the *New England Journal of Medicine* for May 22, and he also published two historical papers based on our collections, "The War of 1812 and the Marine Hospital for the Port of Boston," in the *Bulletin of the History of Medicine* for June, and "The Problem of the Three Edward Warrens," in the *New England Journal of Medicine* for June 19. The death of Sir D'Arcy Power on May 18, an old friend of the Library, and indeed of all medical libraries and

historians, was noted in an exhibit of books, pamphlets, pictures and letters in the rotunda and an obituary in the *New England Journal of Medicine* for July 3.

The Book Review Department, thanks to the generosity of the *New England Journal of Medicine* and our fellows and friends who review the books, continues to function in a satisfactory manner.

In the last year, the cataloguing of the Storer Collection of Medals has been brought up to date, listing all the accessions since the late Dr. Malcolm Storer issued his catalogue of the whole collection in 1931. Valuable additions have been made in the last few years, particularly the twenty nine large plaques designed by Pierre Jean David (1789-1856), usually called David d'Angers. This French sculptor worked in Paris at the beginning of the nineteenth century. Many famous men and women sat for him. A nearly complete collection, originals and copies, is in the Musée David at Angers. Of particular interest is his monument to Gutenberg at Strasbourg. The medallions in our collection are of contemporary physicians, many of them well known in the history of medicine.

In 1941, our special collections were increased by modest accessions, largely through purchase by funds set up for the purpose. We have added twoscore incunabula to our growing list, now widely recognized as a group of books of national importance and becoming more widely used each year by scholars. American, English, Spanish and other imprints have been acquired, helping to round out our collection in fields of particular interest.

Of all the book auctions and sales that occurred in 1941, two have particular interest for us. On three days in June, the library of Sir D'Arcy Power was sold at auction by Sotheby and Company, of London. We received only four items out of two-score bid for by cable. The prices in general were well maintained, some of the items selling for high figures. We obtained a good copy of the 1585 edition of Clowes's, *A Brieve and Necessary Treatise . . .*, and the first collected (1639) edition of John Woodall's *The Surgeons Mate . . .*

Another and still more unusual sale occurred at Gimbel Brothers in New York City on October 27. Many of the books offered were sold before the sale actually opened, and fortunately we had arranged with a New York dealer to purchase four books for us. The most significant was the *Prognosticon* (1483) of Dominicus Maria de Novaria, the only copy in America. The books were offered at bargain prices marked with sums such as \$197.50. It seems unlikely that incunabula have ever been sold in a department store before.



The collection was part of the books assembled by O. H. F. Vollbehr, another section having been previously disposed of to the Library of Congress.

As usual, there have been special donations to the Library in 1941. One of the most important is the watch formerly owned by Dr. Amos Holbrook, of Milton, the vaccinator, and his honorary diploma of 1814 from the Massachusetts Medical Society.

In previous years, the Librarian has pointed out a course for the future growth of the Library and its sister institutions. Plans must be held in abey-

ance in wartime, but this does not mean that such plans should be abandoned. The whole library situation in Boston still presents the same problem and will do so even more acutely after the completion of the war. It is well to retain in mind the basic principle of a central reference library, with working units in various medical schools and hospitals. Only on such a broad foundation can the problem be solved. In this solution, the Boston Medical Library should ever retain a vital interest.

HENRY R. VIETS, *Librarian*

## UNRECOGNIZED TYPHOID CHOLECYSTITIS AS A SOURCE OF HOSPITAL INFECTIONS\*

A. DANIEL RUBENSTEIN, M.D.†

BOSTON

**A**CUTE infection of the gall bladder complicating the course of typhoid fever has frequently been noted since the report of Gilbert and Girode<sup>1</sup> in 1890. Similarly, the chronic cholecystitis associated with the typhoid-carrier state has been definitely established as a clinical entity. Thus, although the predilection of the typhoid bacillus for the gall bladder has been sufficiently emphasized, a diagnosis of chronic cholecystitis is usually made without the realization that in a definite number of these cases *Eberthella typhosa* may be the etiologic agent. When such patients are admitted to surgical wards for operative procedures, hospital personnel are exposed to unrecognized typhoid carriers for varying intervals of time. Similarly, in rare cases, acute cholecystitis complicating typhoid fever may also find its way into hospitals without recognition of the basic etiology. The recent epidemiologic investigation of two such hospital infections is considered of sufficient interest to merit discussion.

### CASE REPORTS

**CASE 1.** Dr. R. S., a 25-year-old married house officer, was admitted to the medical service of his own hospital on December 16, 1941, with complaints of malaise, generalized pains and aches, and fever. He had been perfectly well until 3 days prior to admission, when he had noticed that he tired easily. The temperature at this time was normal. In 24 hours, the patient became aware of generalized pains and aches associated with slight soreness of the throat. On the following day, when it was found that the temperature was elevated, he was admitted to the hospital. On admission, physical examination was essentially negative except for diffuse redness of the throat.

Examination of the blood showed a red-cell count of 5,700,000 with a hemoglobin of 96 per cent, and white-

cell counts varying from 3500 to 7300; the blood smear showed 69 per cent neutrophils, 20 per cent lymphocytes, 10 per cent mononuclears and 1 per cent eosinophils. Urinalysis was negative. The blood serum agglutination reactions against typhoid fever showed a gradual rise in titer from + in a dilution of 1:40 on December 17 to ++ in 1:320 on January 6. A blood sample submitted for a Widal test to the State Laboratory was reported positive on December 30. A stool culture was positive for *E. typhosa*.

The temperature remained elevated for about 10 days. The course was mild and uneventful except for an attack of acute right-upper-quadrant pain on December 25. The pain was severe and radiated to the right back and side, and was relieved only after the administration of morphine. The attack was associated with spasm over the region of the gall bladder. Tenderness in the right upper quadrant persisted for 5 days. The temperature became normal on the 11th hospital day. There was no recurrence of gall-bladder symptoms. The diagnosis was typhoid fever.

**Epidemiologic investigation.** To establish a source of infection, attention was directed first of all to the familial contacts of the patient. There was, however, no history of previous typhoid fever among the several members of his own family or that of his wife. Laboratory study of these contacts was entirely negative. The presence of a recent case of typhoid fever on the medical wards of the same hospital was then considered as a possible source of infection. The house officer denied any contact with this case. There was a history of at least two meals away from either his home or the hospital in the month prior to infection. Since no other cases had been associated with the restaurants named, this did not seem an important clue. The possibility of a missed case of typhoid fever was then considered as a source. The patient could, however, recall no recent case of either unexplained fever or peritonitis of unknown etiology. Inquiry was then made regarding patients with gall-bladder disease treated on his wards within the 4 weeks preceding onset. The records revealed 4 such cases during that time. The house officer was particularly aware of 1 patient, Mrs. R. G., who had had an operation for chronic

\*This investigation was conducted in co operation with the Boston Health Department.

†Epidemiologist, Division of Communicable Diseases, Massachusetts Department of Public Health.

cholecystitis and who subsequently had a second operation for stone in the common duct. There was persistent bile drainage following both operations. The house officer had frequently changed the dressings of this patient. In addition, he had helped prepare cocktails for her made from her own bile. The admission and discharge dates in this and in the 3 other recently operated gall bladder cases were obtained. Visits were then made to the homes of these persons, and blood and stool specimens were obtained. Two of these 4 patients gave a past history of typhoid fever. One of these was Mrs. R. G., who had had the disease about 40 years previously. The Widal test and stool culture of specimens from this patient were both positive for *E. typhosa*. Stools in the remaining 3 cases were negative.

**Source case.** Mrs. R. G., a 48-year-old woman, was admitted to the surgical ward on October 20, 1941, with a chief complaint of recurrent upper abdominal pain and jaundice. Her first attack occurred 20 years previously, and was followed by several such episodes for about a year. The patient was then "symptomatic" until about a year prior to admission, when there was sudden onset of jaundice followed in 24 hours by severe cramp-like pain in the upper epigastrium radiating posteriorly to the interscapular region. There were several subsequent attacks, which came on approximately once a month until 4 months before admission. One month prior to entry, attacks began to occur once each week, the last being 17 days before admission. X-ray studies performed by the patient's physician revealed gallstones.

Physical examination showed a slightly jaundiced middle-aged woman in no apparent distress. The only significant physical finding was a minor degree of jaundice of the skin and sclerae. Examination of the blood showed a red-cell count of 4,550,000 with a hemoglobin of 90 per cent, and a white-cell count of 4500, the blood smear showed 59 per cent neutrophils, 32 per cent lymphocytes, 3 per cent mononuclears, 4 per cent eosinophils and 2 per cent basophils. The bleeding time was 3½ minutes, the clotting time 5½ minutes, and the prothrombin time 13.5 seconds. The icteric index was 18. Urinalysis was negative except for an occasional slight trace of albumin. The hospital diagnosis was chronic cholecystitis with cholelithiasis.

On October 22, the patient underwent cholecystectomy. Many stones were found in the common duct. Postoperative cholangiograms confirmed the operator's impression of residual common duct obstruction. The stools were clay-colored at several examinations. There was drainage of about 4 cc. of bile daily.

The patient's condition remained unchanged until November 22, when a second operation was performed, and the common duct was re-explored. Many stones were removed. Following the second operation, there was a large amount of biliary drainage through a T tube and through the wound. The biliary drainage through the T tube persisted throughout the hospital stay and continued even after discharge. Cholangiograms following the second operation suggested a stone in the terminal portion of the common duct. The patient was discharged on December 12, 1941.

**CASE 2.** Miss M. C., a 22-year-old affiliated student nurse, was admitted to the medical ward on January 2, 1942, with complaints of headaches, chills, nausea and vomiting. She had been well until 2 days before admission, when she developed a headache and began having chilly sensations. Later that day, she became nauseated and vomited watery material. The next day, the head

ache persisted. The patient complained of backache. Although she was still nauseated, there were no other gastrointestinal complaints. The past history was not important except that the patient had received a course of antityphoid inoculations early in her training course, approximately 2 years and 2 months prior to the onset of this illness.

On admission, the temperature was 101°F, and the pulse 90. Physical examination was negative except for slight redness of the throat and harsh breath sounds, with scattered coarse rhonchi over both lung fields.

The white cell counts varied from 6400 to 3900. The hemoglobin was 85 per cent, and the smear showed 74 per cent neutrophils and 26 per cent lymphocytes. Urinalysis was negative. Blood culture on January 4 was positive for *E. typhosa*. A positive Widal reaction in a dilution of 1:160 was reported on January 8. The temperature was elevated until January 15. The course was mild, and the patient made an uneventful recovery. The diagnosis was typhoid fever.

**Epidemiologic investigation.** The epidemiologic investigation of this case revealed that the patient had worked, during the 4 weeks preceding the onset of her illness, on a single surgical ward. Inquiry was then made concerning possible missed cases of typhoid fever or surgical cases that might have been of typhoid origin. This brought up for consideration 3 patients with gall bladder disease who had recently been treated on that ward. All 3 had been discharged, and home visits were made to establish a possible typhoid etiology. One, Mrs. S. R., a 28-year-old housewife, who had undergone cholecystectomy on December 7 following a diagnosis of acute cholecystitis, had a positive Widal reaction on January 21. She had been discharged from the hospital on December 27. A stool culture from this patient, taken on January 21, about 6 weeks following operation, was positive for *E. typhosa*. However, the history did not disclose a previous attack of typhoid fever. This, in addition to the fact that she was only 28 years old, made it appear unlikely that the patient was a typhoid carrier. A careful review of her recent hospital admission revealed an acute febrile illness, with symptomatology and a white cell count compatible with the diagnosis of typhoid fever complicated by acute cholecystitis. The student nurse had frequently changed the surgical dressings of this patient following her operation. The discovery of this previously unrecognized case of typhoid fever necessitated the search for the ultimate source of infection among the contacts of the newly discovered case. One such contact, her 64-year-old mother-in-law, gave a history of typhoid fever 25 years previously. For several years, the mother-in-law had had recurrent attacks of right upper-quadrant pain, together with other symptoms usually associated with chronic disease of the gall bladder. It was also learned that 5 years previously, while she was visiting the family of a daughter residing in Canada, her son-in-law had developed typhoid fever. Laboratory study of this suspect revealed that she was a chronic typhoid carrier and was therefore the source of infection for Mrs. S. R., who in turn infected the student nurse.

**Source case.** Mrs. S. R., a 28-year-old housewife, was admitted on December 6 with a chief complaint of right upper quadrant pain of 1 day's duration. About 3 weeks before admission a severe upper respiratory infection, associated with heaviness of the chest and productive cough, appeared. About a week later, the patient noticed that she tired more easily than usual. Her arms and

legs felt heavy. She could scarcely "stand on her legs." After this feeling of tiredness had persisted for about a week, she found her temperature to be 104°F. She consulted a physician, who advised bed rest. The fever persisted. On December 1, she became aware of a dull ache in the right upper quadrant. This subsided until 24 hours prior to admission, when the pain returned with increasing severity. It was intense and colicky, and radiated to the back. She became nauseated and vomited several times. There was no jaundice or clay-colored stools. The past history revealed an attack of right-upper-quadrant pain 1 year previously that had lasted for 3 days.

On admission, the temperature was 103.4°F., and the pulse 120. Physical examination revealed an alert, feverish, restless woman in obvious distress. General examination was otherwise negative except for spasm and tenderness in the right upper quadrant. Examination of the blood showed a white-cell count of 8050, a red-cell count of 4,130,000 and hemoglobin of 70 per cent. Urinalysis was negative. The icteric index was 11.

On December 7, the gall bladder was removed under spinal anesthesia. It was tense, edematous and inflamed, with several small areas of necrosis. No stones were found.

Following operation, the patient ran a spiking temperature. On December 9, 2 days after operation, the white-cell count was 9000. The temperature on that day was 101.4°F. The temperature gradually subsided and was normal on December 24. Except for the temperature, the course was uneventful, and the patient was discharged on December 27. The hospital diagnosis was acute cholecystitis.

### DISCUSSION

The epidemiologic investigation in Case 1 revealed that a house officer on a surgical ward developed typhoid fever following contact with a patient with chronic cholecystitis who was subsequently found to be a typhoid carrier. Investigation of Case 2 showed that a student nurse on a surgical floor in another hospital had developed the disease while taking care of a recently operated case of acute cholecystitis, which was found actually to be typhoid fever manifested by acute cholecystitis. The symptoms associated with the acute gall-bladder attack distracted attention from the basic disease, typhoid fever. The occurrence of acute cholecystitis as the outstanding feature of typhoid fever has been reported in the literature.<sup>2</sup> It has also been shown that acute involvement of the gall bladder, which is occasionally associated with typhoid fever, may progress to perforation.<sup>3</sup>

It has been demonstrated that stool cultures submitted by typhoid carriers subsequent to cholecystectomy become negative in most cases within a few days to three weeks after operation.<sup>4</sup> However, the stool culture may remain positive for a much longer time and may eventually become negative. In the source case, Mrs. R. G., a positive stool was obtained as late as seven weeks after the second operation. All subsequent cultures of the stools and bile, including those grown in an enrichment medium, have been negative. Thus, the

evidence indicates that the carrier condition in this case has been cured.

It is difficult to say whether or not the stool culture obtained from the second source case, Mrs. S. R., will continue to be positive. Since the gall bladder has been removed, it is very likely that she will become noninfectious in a short time. One wonders whether she might have become a carrier if the operation had not been performed. Garbat<sup>5</sup> showed a high incidence of carriers among patients with typhoid fever who manifested symptoms of cholecystitis either as a complication during the disease or as a sequel during convalescence.

It is an interesting coincidence that a similar mode of infection should have been demonstrated in 2 cases of typhoid occurring within a few weeks of each other in two different hospitals. This raises the question of how often typhoid bacilli are associated with chronic disease of the gall bladder. Isolated reports demonstrating this relation are not infrequent. In 1941, Botsford<sup>6</sup> reported a patient with suppurative cholecystitis who, on admission to the hospital, was found to be a chronic typhoid carrier. Too much reliance cannot be placed on older studies that attempted to demonstrate the frequency with which typhoid bacilli occurred in chronic disease of the gall bladder. It is to be expected that improved bacteriologic technics will be more successful in culturing this organism. More recently, Dickinson<sup>7</sup> stated that in a study of the bile of patients coming to operation for gall-bladder disease it was found that 10 per cent are of typhoid origin. A similar study is now being carried on by the Massachusetts Department of Public Health.

It has been demonstrated that cholelithiasis frequently accompanies chronic gall-bladder disease of typhoid origin. Garbat<sup>5</sup> reported in 1922 that stones were found in 3 out of 21 cases that went to operation. Förster,<sup>8</sup> in an analysis of several hundred carriers, found the same proportion of gall-stone sufferers. However, criteria for the carrier state are more rigid today than they were twenty or thirty years ago. Many patients formerly classed as carriers are now considered convalescent typhoid cases. Thus, Bigelow and Anderson,<sup>9</sup> in 1933, noted that, in 12 carriers coming to operation, stones were found in all. The question of the cause of stone formation in typhoid gall-bladder carriers is beyond the scope of this paper. However, the symptoms associated with the presence of gallstones often serve as a valuable lead to the epidemiologist attempting to seek out a source of infection among the contacts to a case of typhoid fever.

The protection of hospital personnel against typhoid fever is a problem that deserves consid-

erable attention. The unrecognized case of typhoid cholecystitis is not the only form of surgical typhoid that finds its way into hospitals without a realization of the typhoid etiology. Typhoid fever is protean in its clinical manifestation. At present levels of incidence, typical cases are uncommon. Of those reported, many are decidedly unusual in their clinical manifestations, and as a result, a patient may be hospitalized for many days before a diagnosis is made and proper precautions instituted to prevent secondary cases.

For many years, it has been a recommended procedure in hospitals to inoculate members of their personnel, including physicians, nurses, laboratory workers and ward attendants, against typhoid fever. In addition to the primary series of three injections, a stimulating dose of 0.5 cc must be administered each year to maintain a sufficient degree of immunity. Recent reports from the Army Medical School<sup>10</sup> indicate that 0.1 cc of typhoid vaccine, given intradermally as the stimulating dose, offers an excellent level of immunity. The intracutaneous route eliminates practically all the constitutional reactions. The intradermal method has also been advocated by some<sup>11</sup> as the method of choice for primary inoculation. However, all observers<sup>12</sup> are not in accord concerning the superiority of the intradermal route. It is still generally recommended that the initial series of three injections be given subcutaneously.

In Case 2, the patient had received the initial series of typhoid inoculations two years and two months previous to the onset of the disease. The stimulating dose had not been administered. One wonders whether the mildness of the clinical course may have been the result of previous immunization.

The house officer, Case 1, had never received antityphoid inoculations. It is apparent that many interns in Massachusetts hospitals do not receive the protection afforded by typhoid vaccination. Whereas immunizing procedures for nurses are often carefully supervised, house officers are left to shift for themselves in this respect. When schedules are drawn up to immunize hospital personnel, it is essential that house officers be included.

In the management of gall bladder cases on hospital wards, attention must be given to the possibility that a definite number may be of typhoid origin. The practicability of routine stool cultures on all such cases has not yet been definitely established. Further studies, utilizing modern cultural methods, will demonstrate what yield may be expected by this method of attack. The possibility of employing the Widal reaction as a screen merits further investigation. According to this procedure, stool cultures would be submitted only by patients who show some

reaction in the Widal test. At present, a practical approach is to establish in every case of gall bladder disease whether there is a history of typhoid fever or of an unexplained fever consistent with this disease. Whenever a case of chronic cholecystitis presents a past history of typhoid fever, the patient should be kept on precautions until laboratory studies exclude the carrier condition. When such cases are admitted to hospitals for elective surgery, it is preferable that the laboratory work be done prior to hospital admission. In many cases, it will be found that the history of typhoid fever dates back many years. Such an interval does not exclude a carrier condition, since it has been shown that the carrier state may exist for an indefinite number of years until cured by operation.<sup>13</sup> Since a fair proportion of chronic carriers do not present a past history of typhoid fever, extreme care should be exercised by all persons handling dressings and discharges from all gall bladder cases. Hospital personnel in charge of these cases must constantly bear in mind that a certain proportion of all cases of chronic cholecystitis are of typhoid origin.

#### SUMMARY

Two cases of typhoid fever that occurred among the personnel on the surgical wards of two different hospitals are presented. The epidemiologic investigation of the first case revealed a previously unrecognized typhoid carrier as the source of infection. The carrier had been admitted for operation with a diagnosis of chronic cholecystitis and cholelithiasis. The epidemiologic investigation of the second case revealed as the source of infection a missed case of typhoid fever admitted to the hospital for a complicating acute cholecystitis; this primary case was in turn traced to a chronic carrier, the ultimate source.

Protection of hospital personnel by routine antityphoid inoculation is an essential preventive measure in all hospitals.

When cases with gall bladder disease are admitted to hospitals for operative procedures, careful histories should be obtained regarding previous typhoid fever. In cases presenting such a history, laboratory studies should be instituted to rule out the typhoid-carrier state.

The possibility of typhoid etiology should be considered in all cases of chronic cholecystitis. Acute cholecystitis may in rare cases be the most outstanding clinical manifestation of typhoid fever.

#### REFERENCES

1. Gilbert A. and Girault J. Contribution à l'étude bactériologique des typhoïdes. *Semaine méd.* 10:431 1890.
2. Paton Mayer C. and Monsell R. Cholelithiasis aguda manifestata in mononucleotica de una febre tifoidica. *Semana med.* 21:1583 1955.
3. Bodnar T. Über einen Fall von Durchbruch der Gallenblase bei kindlichem Typhus. *Zentralbl. f. Chir.* 64:2522-2574 1937.

still remaining in the circulation after the injection and the increasing amount of antibody that the organism develops. When the two factors come into a certain relation with one another, serum disease occurs. In most of the cases, serum disease begins between the seventh and fourteenth days and usually lasts from two to seven days. Sometimes, however, the onset is earlier than this, — on the sixth day or on the fourth day, or even on the second day, — when it is referred to as an "accelerated" reaction. When it occurs during the first day, or perhaps during the first hour, it produces a clinical picture that is quite the same as that in the anaphylactic reaction described above. The point to observe is that there is no sharp clinical boundary between the normal response — serum disease — and the more rapid and violent reaction, or anaphylaxis.

The symptoms of serum disease are well known. Urticaria and joint pains, which are the commonest, depend on a sudden edema of the skin or of the joint structures. Edema may also develop in nerves and thus produce neuritis, as reported by Hoagland,<sup>12</sup> Brahdy<sup>13</sup> and Bennett.<sup>14</sup> Lemierre's<sup>15</sup> patient developed cerebral symptoms, with loss of consciousness and aphasia. Clog<sup>16</sup> described several patients who developed abdominal pains severe enough to indicate operation for "appendicitis." Swelling of the mesenteric lymph nodes and hyperemia of the peritoneum were found.

The difference between the two types of response depends on the degree of individual reactivity. In anaphylaxis, the first dose stimulates the production of antibodies, which then persist in the blood or tissues or perhaps in both, instead of disappearing slowly as they do in most cases. In serum disease, antibodies develop slowly during the incubation period and reach their maximum immediately after the clinical symptoms have disappeared. They are often in high concentration and can be demonstrated in various ways — by the skin tests, by the precipitin reactions and by injection of the patient's serum into the skin of a normal person and subsequent tests of the prepared site (this is the so-called "Prausnitz-Küstner reaction"); or the patient's serum can be used to transfer sensitiveness to a guinea pig. This easy demonstration by various methods is quite different from what one obtains in the naturally sensitive person described below.

These laboratory findings easily explain why it is so very dangerous to administer a second dose of serum shortly after the occurrence of a serum disease. The high degree of sensitiveness of these patients is not so very surprising. Freedman<sup>17</sup> reports a typical case, in which a six-year-old boy received a dose of diphtheria antitoxin and ten days later developed serum disease — almost as

expected. Twenty days after that, he was tested at the clinic for his sensitivity by intracutaneous injection of a dose of 0.05 cc. of horse serum. Within two minutes, he developed a generalized urticaria and then severe asthma. In spite of heroic doses of adrenalin and treatment in a Drinker respirator, he died in about eight minutes.

Blotner<sup>18</sup> describes a twenty-two-year-old man who had been given a dose of tetanus antitoxin three years before receiving 1500 units of the same antitoxin intramuscularly. There was no immediate response, but eighty minutes later the patient developed a generalized itching with a rash. Adrenalin was given at frequent intervals, at first subcutaneously and later intravenously. He became cold and clammy. The blood pressure fell to 80 systolic, 40 diastolic. In five hours, the patient was taken to the hospital in an ambulance where fluids were administered in large quantities, and he recovered. This was an accelerated reaction due to the preliminary treatment.

Ferguson<sup>19</sup> reports the case of a six-year-old boy who was injured by an automobile and was given three minims of tetanus antitoxin, followed by a complex barbiturate drug (Evipal) intravenously. He went to sleep but in fifteen minutes suddenly had trouble with his breathing. Twenty-five minutes later, a large wheal appeared at the site of the antitoxin injection and spread all over the arm. Another complex drug (Coramine) was administered, with little benefit. The injection of 10 per cent glucose in saline solution intravenously helped at first so that in two and a half hours the patient was transferred to the hospital ward. An hour later, however, he suddenly stopped breathing. Death was considered to be due to anaphylaxis, but I wonder whether the drugs may not have played a major part. At autopsy, the trachea and bronchi were filled with frothy sanguineous material, and almost all the two lower lobes showed hemorrhagic consolidation.

### *Allergic Reactions*

Allergic reactions occur only in persons who have a certain taint (probably inherited) that gives them a special capacity to develop sensitiveness. They appear to be "naturally sensitive." They usually give a past or familial history of eczema, hay fever or asthma. This is the important group, for serious and sometimes fatal reactions can follow what appears to be the first dose of serum. There may be no history of previous contact with the same foreign substance. The reaction appears to come out of a clear sky except for the fact that further study often reveals the allergic background and the allergic constitution of the patient.

In 1931, I<sup>4</sup> reviewed the cases of several patients who died in a few minutes following a dose of serum that was evidently the first. Since that time, however, many accidents have been reported, but not many of them were fatal.

*Incidence of serum reactions.* How often do serum reactions occur? The literature has been reviewed by Tuft,<sup>20</sup> Zinsser et al,<sup>1</sup> Harten and Walzer<sup>21</sup> and more recently, in a very comprehensive article, by Rutstein and his associates.<sup>22</sup> According to the last authors, immediate serum reactions can be grouped on a clinical basis into three definite classes. Thermal reactions (fever and chills) occurred as the only response in 218 patients, or 9 per cent of the total of 2340, treated with a concentrated, type-specific antipneumococcus horse serum by intravenous injection. Anaphylactic reactions, with itching, urticaria, asthma, angio-neurotic and, sometimes, laryngeal edema, occurred in 5 per cent. Circulatory reactions, with a rapid, thready, irregular pulse, shock and, sometimes, vascular collapse, occurred in 3 per cent. And, finally, miscellaneous reactions—nausea, vomiting, headache, lumbar pain and dyspnea without asthma—occurred in 4 per cent. Combinations of these reactions were observed in an other 10 per cent, to make a total of 32 per cent of the patients who developed reactions of one type or another. In another paper,<sup>23</sup> the same authors point out that reactions of all types are commoner with a history of asthma (455 per cent of 101 cases) than they are without such a history (29.6 per cent of 3114 cases). Obviously, the allergic background is always significant, and one should ask each time for evidences of allergy, such as hay fever, asthma and eczema, in the patient and in his family.

The incidence of serum reaction is shown by many figures in many papers. It is, however, not profitable to study them too closely or to attempt any direct comparison between the different reports. As Fox<sup>24</sup> says, variations in the proportion of reactions depend on many different factors, the degree of sensitiveness of the patient under treatment is one; his age is another. The particular lot of serum used may be a third factor. It is known, for example, that the serum from one particular horse may give a larger proportion of reactions than another lot of serum, and the commercial laboratories accordingly pool the serums from different animals. The route by which the serum is injected changes the figures. In the early days, when Park<sup>25</sup> reviewed the treatment of diphtheria by antitoxin, he found that death due to the serum had occurred in only 5 cases among a total of 350,000 children treated. In those days, the doses were of straight horse serum and were

given subcutaneously in amounts varying from 5 to 15 cc.

The serum treatment of pneumonia is given by the intravenous route, and the incidence of serum disease depends on the quantity injected. Before methods of concentration were employed, this serum was given in quantities of 100 cc. or more, and delayed reactions (serum disease) occurred in at least 90 per cent of the cases. At present, practically all serums are concentrated. As a result, Lord and Heffron<sup>6</sup> have found the incidence of serum disease to be much lower: it occurred in only 20 per cent of 1423 patients recovered from pneumonia with serum treatment. When scarlet-fever antitoxin was used in crude form, serum disease occurred, according to Toomey and Baker,<sup>26</sup> in 38.5 per cent of 283 patients, but when concentrated antitoxin was employed, it developed in only 11 per cent of 524 patients.

Rabbit serum was first used by Horsfall and his associates<sup>27, 28</sup> at the hospital of the Rockefeller Institute as a treatment for pneumonia. In 1937, they treated 22 patients with doses varying from 32 to 268 cc. Twenty one recovered from the pneumonia, and a mild serum disease developed in 12 (57 per cent). In 1938, the same authors, in a report on 67 cases of pneumonia treated with rabbit serum, observed that except in Type 3 pneumonia the mortality was as low as 37 per cent. Serum disease occurred in 40 per cent. This figure, however, was much less than that when horse serum was used in the same hospital. Unconcentrated horse serum produced serum disease in 95 per cent of 100 consecutive cases. Rabbit serum, therefore, not only appears to be better than horse serum as a conveyor of antibodies, but produces serum reactions much less frequently. It should be very useful for patients who need serum treatment and yet are sensitive to horse serum. Volini and Levitt<sup>29</sup> also used rabbit serum. They gave an average of 40 cc. of concentrated antipneumococcus rabbit serum intravenously to 153 patients and found serum reactions in 28 per cent. Wood<sup>30</sup> treated 50 pneumonia patients with quantities of immune rabbit serum varying from 10 to 150 cc. injected intravenously. He observed chills and fever reactions in from 26 to 50 per cent, and serum disease developed later in 41 per cent of these cases—an incidence similar to that noted by Horsfall et al.<sup>27, 28</sup> Meanwhile, one should note that it is not the quantity of total protein that is important: it is the specificity. Fox<sup>24</sup> found that pooled human convalescent serum used for the treatment of scarlet fever produced reactions in only 1 per cent of 420 patients.

Recently, Coghill and his associates<sup>31</sup> have described a method of "despeciating" serum by split-

ting off the carbohydrate complex with enzymes like takadiastase; they contend that the product retains about half its diphtheria antitoxin content, whereas it loses its capacity to sensitize guinea pigs to horse serum. Top and Watson<sup>32</sup> have treated 61 children with despeciated antitoxin. Although these patients were selected deliberately as a bad group presumably sensitive to horse serum, serum reactions occurred in only 10 per cent.

### *Reactions to Tetanus Antitoxin*

Tetanus antitoxin causes reactions that are entirely similar to those after diphtheria antitoxin or antipneumococcus serum. Newell and McVea<sup>33</sup> have analyzed 500 patients who were given prophylactic doses of tetanus antitoxin; 59, or 11.8 per cent, developed some type of reaction. Local urticaria developed in every case at intervals varying from a few minutes to two days. Serum sickness, however, occurred in only 22 patients (4.4 per cent). This low figure is probably explained by the relatively small amount of horse serum injected. Schaeffer and Myers<sup>34</sup> treated a patient who had active tetanus and who was so sensitive to horse serum that even tiny doses could not be tolerated. Despeciated tetanus antitoxin was obtained and was injected in slowly increasing amounts, at first intracutaneously, then subcutaneously and finally intravenously. No reactions occurred, and later it was possible to give 10 cc. of the undiluted material intravenously and with no reaction. A total of 140 cc. was injected in various doses, and the patient recovered.

### **P**REVENTION AND TREATMENT OF SERUM REACTIONS

The prevention and treatment of serum reactions are accomplished best by care in the selection of cases and in the administration of serum. Drugs have been tried, but no one of them is very successful. As a method of prevention, Lucchesi and Bowman<sup>35</sup> gave ephedrine and then combinations of ephedrine and calcium in regularly repeated doses to a group of patients; this regimen was begun at the time when the foreign serum was injected. The incidence of serum disease, however, was only slightly influenced, occurring in 38 per cent of the untreated group of patients and in 33 per cent of the treated group. Horsfall et al.<sup>27,28</sup> have recommended that acetylsalicylic acid (aspirin) be given by mouth just before or at the time of the serum injection, but they do not state the dose or present evidence that it does good.

After serum disease has developed, there is not very much that can be done about it. Furthermore, the effect of any treatment is hard to evaluate because the disease is not always long and one cannot be quite sure that the patient who does well with treatment may not also have done well with-

out treatment. Stout and Kisotchek<sup>36</sup> gave hypertonic glucose to 10 patients with serum disease, with some relief. Foshay and Hagebusch<sup>37</sup> used histaminase, saying that 20 out of 22 unselected patients were relieved by the material, which was given sometimes by mouth, sometimes by intramuscular injection and sometimes by both methods together.

A very thorough presentation of the technical details of this subject, including general rules to be followed in the administration of therapeutic serums, is given in a special article prepared by Fantus and Feinberg<sup>38</sup> for the *Journal of the American Medical Association*. As soon as the principles are understood, these rules become almost obvious. Before any foreign serum is injected, it is essential to ask two questions. The first is, Have you ever had serum given to you before? The reason for the previous dose, the type of serum used and, especially, the presence or absence of serum disease after this earlier treatment are important details. The second question is, Are you allergic? That is, has the victim ever had hay fever, asthma or eczema, or has anyone in his family ever had one or another of these symptom complexes?

A test for serum sensitiveness should always be made. There are several methods. A scratch is made with a sharp needle or knife point through a drop of the serum. It should be controlled with a similar scratch through a drop of physiologic saline solution or of water. An intracutaneous test is much more delicate, but may give false-positive reactions unless the serum is diluted ten or even one hundred times with physiologic saline solution. Again, the test should always be controlled with similar injections of something else, such as egg white in a 1:100 dilution or ragweed extract in a 1:1000 dilution, but saline solution alone usually suffices—made with the same syringe beforehand or, better, with another perfectly clean syringe. With both the scratch and the intracutaneous methods, reactions appear in ten or fifteen minutes as typical urticarial wheals, with sharp advancing borders and surrounding erythema or redness. They should be interpreted with due regard for the control reactions.

One performs eye tests by applying a drop of the serum, diluted 1:10 with physiologic saline solution, directly to the conjunctival sac. When the serum is used undiluted, false-positive, irritative reactions may occur. If the patient is sensitive, the eye becomes red at once, and the reaction may include edema of the conjunctiva. It can be relieved promptly by the instillation of a drop of 1:1000 epinephrine (adrenalin) in watery solution. The intravenous test for sensitiveness has been used by Loughlin, Spitz and Bennett<sup>39</sup> and by

Wood.<sup>30</sup> The former give a small dose (0.1 cc.) of the foreign serum diluted with 5.0 cc. of physiologic saline solution and inject it into the vein slowly. If, during the injection, the blood pressure falls 20 mm. or the pulse rate increases 20 beats, the patient is considered sensitive, and the injection is stopped. One or 2 minims of epinephrine can be injected intravenously through the same needle if severe reactions develop. Wood uses a larger dose, — 1.0 cc. of serum diluted with 20 cc. of saline solution, — and he waits a whole hour for reactions to develop before he proceeds with his therapeutic dose. Obviously, such tests in a highly sensitized patient may result in severe and even dangerous reactions.

The relative value of these different tests — indeed, the real value of any test as an accurate measure of the degree of sensitiveness — is far from clear. In hypersensitiveness, antibodies are attached to cells, and to some cells more than to others. The eye or the skin may be more sensitive, or it may be less sensitive than any other more vital tissues — the bronchial mucosa for example. In an unpublished study in our clinic, Rasch<sup>40</sup> found that the skin test (scratch method) gave good reactions to dilutions of ragweed-pollen extract four to eight times as weak as the lowest strength that reacted in the eye. Tuft<sup>20</sup> has stated that a positive eye test to horse serum never occurs in the absence of a positive skin reaction. Brown and Sechzer<sup>41</sup> compared intradermal and eye tests with rabbit serum in 101 patients in their allergy clinic; in both methods the 1:10 dilution was used. Only 1 patient gave a positive eye test, whereas 32 reacted positively to the intradermal injections, 1 of them being so sensitive that the test alone induced a generalized urticarial eruption. Toomey and August<sup>42</sup> found no fixed relation between the presence or absence of slightly positive skin tests at the time of serum treatment and the subsequent appearance of serum disease. Davis<sup>43</sup> has studied this further. In 200 patients (180 children and 20 adults) ill with diphtheria, she found positive skin tests in 39 per cent. Of those with negative skin tests (61 per cent of the total), 22.1 per cent developed a serum reaction after the administration of antitoxin, whereas of the 39 per cent who were skin sensitive, 28.2 per cent reacted later — the figure was higher, but not much higher.

On the whole, I believe that the history is the vital criterion, but that skin tests should be made as a check on the history. The finding of a positive reaction to horse serum constitutes a significant warning of a danger that is very real. A positive skin test may mean a general sensitivity, but not always, and if the skin reaction is not large it may

be possible to proceed with the treatment, provided that one works slowly and with every precaution. If rabbit or beef serum is available, that can be tried. However, if the reactions to small preliminary doses are severe, one should recognize that to take a chance on the results of failing to administer serum may be better than to kill the victim forthwith. In desperate cases, the patient may be desensitized.<sup>34</sup>

The injection of epinephrine (adrenalin) solution at the same time as the injection of serum, or the addition of epinephrine to a dilution of serum with physiologic saline, is to be considered if sensitiveness is demonstrated. It has two objections: the injection of epinephrine to a nonasthmatic person may induce a severe adrenergic reaction, with shaking, palpitation, rise in blood pressure and even disturbance of the heart rhythm; and the epinephrine may postpone and mask the onset of a reaction until an overwhelming dose of serum has been administered. I believe that epinephrine should not be given until the reaction begins, but that it should then be injected at once. Epinephrine should take effect within five minutes, and the prompt injection of a small dose (0.5 cc. of a 1:1000 dilution) should suffice. To give more than 2.0 cc. of epinephrine hydrochloride subcutaneously in one hour may be dangerous.

#### PREVENTION AND TREATMENT OF TETANUS

##### Prevention

The prevention of tetanus at the time of injury of a person who has not been previously immunized with tetanus toxoid is accomplished best by the prompt administration of tetanus antitoxin, as stated above. However, active immunization with tetanus toxoid, will, it is hoped, be a matter of universal application in the near future. In 1923, Ramon<sup>44</sup> discovered that when diphtheria toxin was treated with formalin, it lost its toxic properties without losing its antigenic capacity, and Descombey<sup>45</sup> found this to be true for tetanus. Ramon and Zoeller<sup>46</sup> published several papers on the use of what they called "anatoxin" to produce active immunity to tetanus in man.

The results from active immunization against tetanus are most satisfactory. Rouques<sup>47</sup> has reported that by May, 1939, approximately 1,500,000 soldiers in France had been immunized with tetanus toxoid, and up to the time of his writing, no case of tetanus had been reported among them. Other and similar reports can be anticipated. When normal subjects are given two injections of alum-precipitated tetanus toxoid at intervals of two to eight weeks, — the average is about a month, — tetanus antitoxin develops in the blood. Gold<sup>48</sup> has shown that the alum-precipitated ma-



terial gives better results than plain toxoid, presumably because it is absorbed more slowly and over a longer period. After the first dose, the response is small, but after the second the antitoxic content increases markedly, as Jones and Moss<sup>49</sup> showed. In an earlier paper, Gold<sup>50</sup> found that this antitoxin content tends to fall again in the course of months. If, however, at the time of injury an additional dose of toxoid is administered to these pretreated persons, the antitoxin returns very promptly, and the titer becomes higher than ever. Since, according to a recent announcement,<sup>51</sup> all United States soldiers are to be immunized against tetanus, only those casualties whose wounds have been grossly contaminated with material suspected of containing tetanus spores will require other than an injection of tetanus toxoid.

Reactions to tetanus toxoid, particularly to the second dose, have caused some difficulty. Anaphylaxis has been reported. In 1940, Cooke and his associates<sup>52</sup> described a forty-four-year-old man with asthma who was given his first dose of tetanus toxoid in June without symptoms. In October, the second dose was followed in fifteen minutes by a constitutional reaction, with severe urticaria, edema of the face and prostration. Skin tests with the pure materials used in making the toxoid were applied, and large reactions were obtained to the peptone used in the broth, as well as to the toxoid itself. In 1940, Parish and Oakley<sup>53</sup> observed a patient who did not give any history of allergy, but who nevertheless reacted in ten minutes in the same way as Cooke's patient did; furthermore, when an intracutaneous test with Witte peptone was applied, another constitutional reaction ensued.

Reactions to tetanus toxoid, however, are not common. Whittingham<sup>54</sup> was able to collect only 14 cases (0.023 per cent) among 61,042 persons immunized with two doses. Hall,<sup>3</sup> who has had a large experience with tetanus toxoid in the United States Navy, says little about peptone as a cause of reaction, but he has observed that one lot of toxoid gave reactions (mostly sore arms) in 50 of 1800 second injections, whereas another lot of toxoid gave no reaction in any of the 743 midshipmen treated. He found that the first lot contained more total nitrogen than the second lot, and that it reacted with the protein color tests. The only difference between the two lots was in the manner in which the alum precipitate had been washed. If the reactions are due to peptone in the broth used for growing this organism, it is very strange that guinea pigs sensitized by Hall's alum-precipitated tetanus toxoid did not react to alum-precipitated diphtheria toxoid or vice versa, whereas members of each group of animals died at once

in anaphylactic shock when reinjected with the original sensitizing material.

Is it always safe to give the second dose of tetanus toxoid? Should one always inject a small quantity of the material into the skin itself, to be sure that there is no reaction, before administering the whole of the second dose? This would be playing safe, of course, but since sensitiveness is so rare and reactions are so few, it is probably sufficient in actual practice to inquire about reactions to the first dose of toxoid and then to consider whether the patient has an allergic history. If there is any doubt, however, a skin test takes only a little time and is very easy to perform.

### *Treatment*

The treatment of active tetanus is always difficult, and the mortality ranges between 30 and 90 per cent according to different authors. As Zinsser, Enders and Fothergill<sup>1</sup> write, "A review of mortality statistics does not impress one regarding the value of antitoxin." They point out: "The effect of antitoxin is probably limited largely to neutralization of uncombined toxin circulating in the blood stream and lymphatics. . . . For this reason, its use as a therapeutic agent is definitely indicated." They condemn the injection of antitoxin either into the spinal canal or into the cisterna, for "to reach the motor cells, the injected antitoxin would have to pass the pial membrane and be absorbed across a large space of tissue." Through the blood stream, however, the serum can reach the motor cells quickly and easily.

Quite recently, three papers described a similar and quite new conception of the treatment of tetanus. These papers were written at about the same time. No one of them refers to the others, and it is quite interesting that each of the authors arrived at about the same conclusions and quite independently. Each uses antitoxin intravenously in large doses and then gives heavy sedation. Vener and Bower<sup>55</sup> advocate an initial dose of 100,000 units of tetanus antitoxin intravenously, and a total dose of about 200,000 units. Of 100 patients, 12 died within the first twenty-four hours of treatment, but of the 88 who survived the first day, only 17 died—a mortality of only 20 per cent. Chapman and Miller<sup>56</sup> give a graphic description of a heroic and victorious struggle with the disease in a boy of ten. They emphasize six principles in treatment. The first is not antitoxin but sedation, and they used large and almost continuous doses of luminal sodium and morphine. The second is surgical removal of the focus, and the third is antitoxin, which they give intravenously in moderate doses, 20,000 to 40,000 units at intervals during the first

few days. Lumbar puncture was used frequently for restlessness and convulsions, evidently because of increased intracranial pressure. Finally, they lay great stress on general care: on oxygen for cyanosis; on aspiration of nasal mucus to clear the airways; on food and water by nasal catheter to maintain nutrition; and on constant attendance by skillful nurses. The third paper is by Spieth,<sup>57</sup> who also uses 30,000 to 60,000 units as a first dose. He too emphasizes heavy sedation and lays great stress on skillful care, with expert attention to every detail of medical and surgical management. In a hospital as large as the Cook County Hospital in Chicago, he advocates special tetanus teams of highly trained nurses. As a result of the new methods of treatment, the danger of tetanus has been modified greatly. The experience in Chicago is a large one, and the conclusions of Spieth deserve attention. Mild tetanus, without convulsions, is not fatal. Moderate tetanus with spasm but without cyanosis occurred in 32 patients, 2 of whom died. Severe tetanus is the real problem. Before the modern technic, 109 patients (95 per cent) died in a group of 114, but with the new methods only 32 (74 per cent) died out of 43. In total, the mortality from tetanus at Cook County Hospital has fallen from 67 to 35 per cent. Whoever is called on to treat a patient with active tetanus should read each of these three papers carefully.

263 Beacon Street

REFERENCES

1. Friesen H, Enders J F, and Forthright L D. *Immunus, principles and application in medicine and public health*. 801 pp. New York: The Van Nostrand Company, 1939.
2. Robertson W E. The prophylactic use of tetanus antitoxin. *Am J Med Sci* 151:693-692, 1916.
3. Hall B W. Tetanus toxoid immunization in United States Navy. *Ann Int Med* 14:565-552, 1940.
4. Rackemann F M. *Clinical Allergy, Particularly Asthma and Hay Fever, Prevention and treatment*. 617 pp. New York: The Macmillan Company, 1931.
5. Wilder G J. The prevention of anaphylactic shock with a study of the fatal cases. *J A M A* 98:446-449, 1932.
6. Lord P Y, and Commons R H. *Penicillins and Serum Therapy*. 148 pp. New York: The Commonwealth Fund, 1938.
7. Quill L M. Anaphylaxis during ether anesthesia. *J A M A* 109:954-957, 1937.
8. Gorcevici A, and Blum P. Phenomene d'Arthus necrotique apres une injection de serum antitetanique. *Arch Dermatol Syph de la Clin de Paris* 10:67-70, 1938.
9. Huxley S B. Human hypersensitiveness induced by very small amounts of horse serum. *J Immunol* 10:10-19, 1932.
10. Gordon J E, and Crenshaw S M. To what extent do toxin antitoxins make us sensitive to therapeutic serum? *J Prev Med* 3:21-30, 1939.
11. Telt L. Serum sensitiveness after toxin antitoxin: a clinical and laboratory study. *J Allergy* 3:235-246, 1932.
12. Houghand R J. Neuritis following serum administration. *Mil Surgeon* 42:134-137, 1938.
13. Erskind L. Musculo spiral paralysis after serum injection (recurring after second injection). *Ann Int Med* 11:911, 1938.
14. Bennett A E. Horse serum neuritis with report of five cases. *J A M A* 112:590-594, 1939.
15. Lemerre A, Laporte A, and Donnat J. Un cas de manifestations cliniques de la maladie serique. *Bull et mem Soc med d hop de Paris* 34:377-380, 1938.
16. Cline M L W. Syndromes douloureux abdominaux au cours de la maladie serique. *Bull Soc de med de Paris* 36:354-364, 1938.
17. Friedman H J. Acute anaphylactic shock following intracutaneous test for sensitivity to horse serum: report of a fatal case. *New Eng J Med* 212:10, 1935.
18. Blatter H. Anaphylactic shock with hemoconcentration treated intravenously with saline solution. *J A M A* 118:219-221, 1942.
19. Fetz G P. A case of fatal serum reaction. *Canad M A J* 43:469-471, 1940.
20. Telf L. *Clinical Allergy*. 711 pp. Philadelphia: W B Saunders Company, 1937.
21. Haxton M, and Walzer, M. Serum allergy. *J Allergy* 11:68-98, 1939.
22. Ruessin D D, Peed, E A., Langmuir, A D, and Rogers E. S. Immediate serum reactions in man: classification and analysis of reactions to intravenous administration of antipneumococcus horse serum in cases of pneumonia. *Arch Int Med* 68:25-36, 1941.
23. Ruessin D D, Rogers E S, and McCaffrey J. The significance of a history of asthma with reference to serotherapy. *New Eng J Med* 225:363, 1941.
24. Fox M J. Relation of incidence of human and animal serum disease. *J Infect Dis* 61:341-344, 1937.
25. Park W H. Is serum anaphylaxis a danger of sufficient importance to limit our use of protective sera in the treatment or prevention of disease? *Tr A Am Physicians* 28:95-102, 1913.
26. Toomey J A, and Paker C S. Treatment of scarlet fever with specific antitoxins of low protein content. *J Pediatr* 12:439-448, 1938.
27. Horsfall F L Jr., Goodner K, MacLeod C M, and Harris A H. Antipneumococcus rabbit serum is a therapeutic agent in lobar pneumonia. *J A M A* 108:1483-197.
28. Horsfall F L Jr., Goodner K, and MacLeod C M. Antipneumococcus rabbit serum as a therapeutic agent in lobar pneumonia. II. Additional observations in pneumococcus pneumonias of nine different types. *New York State J Med* 38:745-755, 1938.
29. Volini I F, and Levitt P O. The treatment of pneumococcus pneumonia with concentrated rabbit serum. *J A M A* 113:1314-1316, 1939.
30. Wood W B, Jr. Treatment of pneumococcus pneumonia with concentrated antipneumococcus rabbit serum. *J A M A* 113:745-747, 1939.
31. Coghill R D, Fell N, Creighton M, and Brown, G. The elimination of horse serum specificity from antitoxin. *J Immunol* 39:20-22, 1940.
32. Topf E H, and Watson E H. Reduction of serum reactions due to antitoxins of which the protein specificity has been altered by enzymic digestion. *Am J Dis Child* 62:248-254, 1941.
33. Newell C A, and McVea C. Prophylactic use of tetanus antitoxin in cases of five hundred cases. *South M J* 33:962-967, 1940.
34. Schaeffer L, and Myers G B. Tetanus in a serum sensitive patient successfully treated with a new despeciated antiserum. *J Allergy* 12:188-190, 1941.
35. Luchette P F, and Bowman J L. Antitoxin versus no antitoxin in scarlet fever. *J A M A* 103:1049-1051, 1934.
36. Stout O M, and Kistochek R J. Parenteral use of hypertonie trousse for relief of pruritus and of serum sickness. *Arch Dermatol Syph* 42:802-807, 1940.
37. Fushay L, and Hagebusch O E. Histamine in the treatment of serum sickness. *J A M A* 117:1938-2402, 1939.
38. Farnus B, and Feinberg S M. The therapy of (horse) serum reactions: general rules in the administration of therapeutic sera. *J A M A* 107:1717-1719, 1935.
39. Loughlin E H, Spitz S H, and Bennett R H. Treatment of lobar pneumonia with rabbit antipneumococcus serum: efficacy of the projected dose method of treating pneumonia with homologous refined and unrefined rabbit antipneumococcus serum. *Arch Int Med* 68:121-133, 1941.
40. Rasch J H O. Unpublished data.
41. Brown A, and Scherzer P H. Sensitivity to rabbit serum. *J A M A* 111:1370-1938.
42. Toomey J A, and August M H. Reactions following administration of diphtheria antitoxin and toxoid antitoxin: results of desensitization. *J Prev Med* 4:251-294, 1930.
43. Davis H M. Horse serum skin tests. *J Hsg* 38:325-330, 1938.
44. Ramon G. Medecine experimentale sur le pouvoir bouclant et sur les propriétés immunisantes d'une toxine diphtherique rendue antitoxique (antatoxine). *Compt rend Acad d se* 177:1333-1340, 1923.
45. Dekombey P. Lanatoxine tetanique. *Compt rend Soc de biol* 91:239-241, 1924.
46. Ramon G, and Zoeller C. L'immunité antitetanique par lanatoxine chez l'homme. *Presse med* 34:482, 1926. De la valeur antigenique de lanatoxine tetanique chez l'homme. *Compt rend Acad d se* 182:245-247, 1926. Lanatoxine tetanique et immunisation active de l'homme vis a vis du tetanos. *Ann de l'Inst Pasteur* 41:803-833, 1937.
47. Rouques L. Le tetanos la vaccination et la sero-vaccination conduite a tenir chez les blesses le debut du tetanos et les tetanos partiels des membres la sero-antitoxine. *Presse med* 48:497-499, 1940.
48. Gold H. Active immunization against tetanus. *Ann Int Med* 13:768-782, 1939.
49. Jones F G, and Moss J M. Studies on tetanus toxoid. II. The response of human subjects to an injection of tetanus toxoid or tetanus alum precipitated toxoid one year after immunization. *J Immunol* 33:183-190, 1937.
50. Gold H. Studies on tetanus toxoid. II. Active immunization of normal persons with tetanus toxoid alum precipitated refined. *J A M A* 109:481-484, 1937.
51. Medical preparedness. Solders identification tags. *J A M A* 118:541-1942.
52. Cooke R A, Hampton S, Sherman W B, and Stull, A. Allergy induced by immunization with tetanus toxoid. *J A M A* 114:1854-1858, 1940.
53. Parham H G, and Oakley C L. Anaphylaxis after injection of tetanus toxoid. *Brit M J* 1:194, 1940.
54. Whittingham H E. Anaphylaxis following the administration of tetanus toxoid. *Brit M J* 1:392, 1940.
55. Vener, H I, and Bower A G. Clinical tetanus treatment in 100 consecutive cases with net mortality rate of 19 per cent. *J A M A* 116:1627-1631, 1941.
56. Chapman E W, and Miller, R. II. The treatment of tetanus. *New Eng J Med* 225:532-536, 1941.
57. Spaulding R. Therapy of tetanus: a study of two hundred and seventy six cases. *Arch Int Med* 68:1133-1160, 1941.

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTE-MORTEM AND POST-MORTEM RECORDS AS USED  
IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

### CASE 28181

#### PRESENTATION OF CASE

A fifty-three-year-old single clerical worker was admitted to the hospital because of nausea.

She had been in good health until a month before entry, when she developed nausea after eating that was occasionally followed by vomiting. The vomiting occurred as often as three times a week, and was not associated with pain, gaseous distress or other symptoms. The bowels were regular, and the appetite was good, although 10 pounds of weight had been lost in the course of the month. A week before entry, a physician prescribed liver and iron therapy; he told the patient that she had been having "glycosuria for several years."

The patient's father died at fifty-nine years "in diabetic coma."

On admission, the patient appeared well developed and nourished, with striking pallor of the skin. The mouth was edentulous. The breasts, heart and lungs were normal. The abdomen was soft, with a movable mass extending upward from a point just below the umbilicus; this seemed to join with a second mass that lay just beneath the left costal margin. The left border of the masses seemed quite discrete.

The blood pressure was 140 systolic, 90 diastolic. The temperature, pulse and respirations were normal.

Examination of the blood showed a red-cell count of 3,150,000 with 8.4 gm. hemoglobin, and a white-cell count of 12,400, with 74 per cent polymorphonuclears, 18 per cent small lymphocytes and 6 per cent monocytes. The blood Hinton reaction was negative. The hematocrit was 33 per cent. The prothrombin time was normal. The urine was normal on two examinations. The stools were guaiac negative.

Roentgenograms of the gastrointestinal tract showed a normal stomach and duodenum. One of the upper loops of jejunum showed pressure of an extrinsic mass; the upper loops were slightly dilated. The two-hour film showed most of the barium beyond a lobulated mass, 15 cm. in diameter, lying in the left midabdomen. One loop of bowel appeared involved by the mass, since this loop retained barium for five hours. The margins

of the bowel were irregular and serrated, and there seemed to be swelling of the mucosa, without definite obstruction. The lower ileum and colon appeared normal, although the mass seemed to press slightly on the upper descending and transverse portions of the colon.

Two days later, additional roentgenograms were taken with a Rehfuess tube passed into the third portion of the duodenum. The first loop of jejunum again appeared dilated. The second loop ran around a mass and showed marked disturbance of its mucosal pattern. No definite folds were seen. Fine sinuses appeared to run away from the lumen. The abnormal area extended approximately 16 cm. The lower small intestine seemed normal, barium reaching the ileocecal valve in twenty minutes.

On the ninth hospital day, an operation was performed.

#### DIFFERENTIAL DIAGNOSIS

DR. ROBERT R. LINTON: I must admit that I have not a great deal to go on in this patient except that she had nausea and vomiting of a month's duration. She was fifty-three years of age and came in with a tumor in the left upper quadrant. The description on physical examination is different from that on x-ray examination, and I think one must realize that in the latter the mass chiefly noted was probably the lower one.

Let us approach this by considering tumors of the left upper quadrant. The first one that enters my mind, since the upper mass was at the left costal margin, is the spleen. I cannot connect the spleen with a mass separate from it and extending below the umbilicus. We have no history of malaria or any other disease that might incriminate the spleen, and I think that the spleen can be ruled out. It is possible that the patient had an aneurysm of the abdominal aorta, but such an aneurysm would not be freely movable and would be a pulsating mass. Therefore, I can rule out aneurysm. It might be a kidney tumor, because kidney tumors can present anteriorly as well as posteriorly, but again we have nothing to incriminate the kidney. The urine examination was negative. No intravenous pyelograms were done, or reported at least; and I therefore think that a kidney lesion can also be ruled out. One must consider a number of conditions in the gastrointestinal tract, but before going on to those I might ask Dr. Holmes to show us the x-ray films. Do you know whether the barium reached the ileocecal valve in twenty minutes after it was taken by mouth?

DR. GEORGE W. HOLMES: I do not believe so. I think the last statement refers to an enema for

the small bowel, which Dr. Schatzki has recently been working on

We have fairly good evidence that this patient had a lesion involving the small bowel and primary either in the small bowel or in the abdomen outside the small bowel. The stomach and colon were normal. There is nothing abnormal about the appearance of the liver and spleen, according to the x ray films. The kidneys are not well visualized. There is no evidence of any disease of the bone. In this first film, one sees dilated loops of small bowel, which are definitely abnormal, and in this one, taken when the barium was leaving the stomach, the loops are rather large and the barium has a tendency to pile up in that area. A little later, one sees retention of barium, and a rather ragged indefinite margin in the same position. In twenty-four hours, there are some traces of barium in the small bowel. From this examination alone, we have very good evidence of a small-bowel lesion. This next group of films, taken after the injection of the barium through the tube, shows a definitely deformed loop of small bowel. Lesions of the small bowel often show quite extensive involvement of the mucosa but do not of necessity produce obstruction. This one did, and there is no question about the involvement of the mucosa. As I read the note, I got the impression that there was some evidence of another lesion in the small bowel, but I cannot find it offhand. The lower small bowel seems to be normal. In other words, I do not believe this is the so-called "ileitis." It does not look like that. It is some form of tumor. It could be tumor outside involving the bowel, or it could be a tumor involving the bowel from the inside.

DR. WILLIAM B. BREED: Can you demonstrate the displacement by the mass that was palpated? I do not see that.

DR. HOLMES: I do not see it either. I think one would have to fluoroscope the patient to be able to visualize it. In these films, it is not obvious.

DR. LINTON: Another condition I had considered is pancreatic cyst, but I believe the fact that the jejunum beyond the ligament of Treitz for a considerable distance is involved rules out the question of pancreatic cyst. Also, the fact that it was movable eliminates, such a cyst, because the pancreas is a rather fixed retroperitoneal structure. The conditions one must consider are: carcinoma, lymphoma, congenital abnormality and infection.

Carcinoma of the jejunum is a fairly rare disease, but it does occur. Carcinoma of the jejunum, however, would produce a localized lesion, with complete obstruction rather than a lesion that extended over perhaps 16 cm of the bowel with only partial obstruction. The other thing

that seems strange, if it should prove to be carcinoma, is that the stools were guaiac negative. Certainly, with an ulcerated lesion, one would expect at least microscopic blood in the stools.

Was this a lymphoma of the small bowel? I am unable to rule it out, and I think that this diagnosis should be seriously considered. The patient had a low red cell count and hemoglobin and not a very significant white cell count.

One other condition that I should consider much more seriously if this were a child rather than an adult is so-called "enteric cyst" or reduplication of the intestinal tract. It seems unlikely that the patient would live fifty three years without getting into trouble from such a cyst, and I think one would have to exclude it on that basis. Then there is the mesenteric cyst, which is different from an enteric cyst or reduplication of the intestinal tract since it is localized in the mesentery instead of involving the bowel wall. That seems to me to be a possibility. The only thing that seems doubtful about that diagnosis is the fact that in the last x ray film fine sinuses appeared to run outward from the lumen of the bowel; this suggests to me that there was destruction of the bowel wall or intestinal mucosa, with sinuses running away from it. I remember a case similar to this in a patient who ate a piece of porcupine quill, which stuck in the upper jejunum and produced an abscess. One can rule out the question of foreign body with abscess because the patient had a freely movable mass, no fever and no leukocytosis.

In conclusion, I believe that this was a lesion of the bowel, involving the bowel wall and the bowel lumen, with partial intestinal obstruction. The only way to be absolutely sure what the condition is is to open the abdomen. I hazard the guess that this patient was suffering from lymphoma of the small bowel.

A PHYSICIAN: Would not the appearance of the serrated small bowel be against anything like cyst?

DR. LINTON: I should think so, except an enteric cyst, and the patient is too old for that.

DR. TRACY B. MALLORY: The X-ray Department expressed a preference for regional enteritis. Do you want to comment any further about that, Dr. Holmes?

DR. HOLMES: I think they had a decided advantage over me, and I hesitate to disagree with them. Of course, with a multiple lesion, enteritis should always be seriously considered.

DR. LINTON: I intended to discuss regional enteritis. It seemed a definite possibility in view of the x-ray picture. The thing against it is the short duration of the history and the localization of the

lesion in the jejunum, although I am aware that it may occur in this location.

DR. CHESTER M. JONES: It tends toward fistula formation.

DR. ALLEN G. BRAILEY: I think we should re-emphasize the points that Dr. Jones and Dr. Richardson made two weeks ago when I discussed a case—namely, guaiac-negative stools do not rule out ulcerative lesions in the mucosa, and furthermore the rather extreme anemia means that the patient had been bleeding, probably for some time.

#### CLINICAL DIAGNOSIS

Lymphoma of jejunum?

#### DR. LINTON'S DIAGNOSIS

Lymphoma of jejunum.

#### ANATOMICAL DIAGNOSIS

Carcinoma of jejunum.

#### PATHOLOGICAL DISCUSSION

DR. MALLORY: Dr. Richard H. Sweet, who operated on this patient, is not here. Can you describe the findings at operation, Dr. Brailey?

DR. BRAILEY: The upper 46 cm. of the jejunum was moderately dilated and injected and quite definitely edematous. Then, about 16 to 18 cm. of jejunum was of normal contour but of smaller size, firm, deep red and speckled with implants. The lymph nodes of the mesentery were involved. The second mass described was a large carcinomatous implant in the mesentery.

DR. MALLORY: The preoperative diagnosis was the same as Dr. Linton's,—lymphoma of the small bowel,—but at operation it was obvious at a glance that it was cancer, primary in the jejunum; that diagnosis was proved by biopsy. It was quite beyond the realm of resection, and a side-to-side anastomosis was done to relieve obstruction.

#### CASE 28182

#### PRESENTATION OF CASE

A sixty-year-old housewife consulted a physician because of numbness in the right leg for a week, and because of various "heart symptoms" of much longer duration.

At least twenty years previously, the patient had been told that she had "heart disease," and on one occasion had been refused life insurance because of it. She frequently visited a health resort. On her last trip to that institution, seven months previously, she had been told that she had auricular fibrillation, with a systolic blood pressure ranging up to 165. At that time, she complained of shortness of breath

on exertion, palpitation and precordial soreness. These symptoms persisted. About six months later, the patient noted for the first time an ache in the upper part of the left arm. This remained constant, becoming worse on exertion. After four weeks, there was a very severe exacerbation of this pain. At about the same time, a cold feeling became manifest in the right leg. This was followed by a persistent numbness in the leg, but no actual pain. During this period, the patient took digitalis.

At the age of twelve years, the patient had "growing pains," but she never was aware of frank rheumatic fever. The family history was of interest, in that the patient's mother died following an amputation for an embolus.

On examination, the patient appeared rather pale, with marked engorgement of the neck veins. The heart was enlarged to the left, with the border of dullness 8.5 cm. from the midsternal line in the fifth interspace. A systolic murmur was heard in the aortic area, without associated thrill transmission to the neck. There was a slight systolic murmur at the apex, with a definite presystolic rumble. The pulse was grossly irregular, at 76. The blood pressure was 135 systolic, 70 diastolic, in each arm, although the pulse seemed stronger in the right arm than in the left. The lungs were essentially normal, as was the abdomen. There was slight pitting edema of the shins. The right leg was noticeably colder than the left. Pulsations of the dorsalis pedis artery were palpable in the left foot, but not in the right. Blood-pressure oscillations were present in both legs, less noticeably on the right than on the left.

An electrocardiogram showed auricular fibrillation, with a rate of 70. The T waves were diphasic in Lead 1, with sagging ST segment, but there was marked and deep inversion of the T waves in Leads 2 and 3. In Lead 4, the R wave was present, and the T wave was diphasic. This record was similar to one taken seven months earlier, except for deepening of the T waves, both in Lead 2 and in Lead 3.

The patient was maintained on digitalis and at rest. After two weeks, she experienced sudden onset of sharp pain over the left chest anteriorly. The respirations became shallow, and were accompanied by pain at the left costal margin and in the precordium, which was relieved by a binder. She then began to have pain in the left leg.

On examination two weeks after the onset of this last set of symptoms (a month after she was first seen), the patient was fibrillating with a rate of 70. The same murmurs were heard as previously described. There was marked bronchial breath-

ing over the left lower-lung field, with dullness. There was slight tenderness in the right calf and over both saphenous veins.

The temperature was normal, and the respirations were somewhat elevated. The blood pressure was 145 systolic, 90 diastolic.

Two days later, the patient complained of pain in the abdomen, without apparent localization. Extreme dyspnea appeared quite suddenly. The patient appeared pale, with cyanosis of the lips and fingertips. Death occurred several days later.

#### DIFFERENTIAL DIAGNOSIS

DR. ROBERT E. GLENDY: We can draw some immediate conclusions from this case history, I believe: the patient had rheumatic heart disease of long standing, with cardiac hypertrophy, mitral-valve and possibly aortic-valve involvement, auricular fibrillation and, for some time, considerable impairment of myocardial reserve, manifested by dyspnea on effort and later by peripheral edema, which may have been the result of peripheral vascular disease; however, toward the end of her life, she had multiple embolic manifestations, presumably from both sides of the circulation.

Although the precordial soreness, pain in the left arm and the bait thrown out in the report of the electrocardiogram tempt one to consider myocardial infarction with mural thrombus formation as a possible source of emboli, the clinical manifestations were too vague, and it is likely that the T-wave changes in the electrocardiogram were due to digitalis instead of myocardial infarction. The patient was well into the coronary age group, but I am willing to discard coronary disease as an important factor. However, an infarct involving the septum of the heart with mural thrombi on either side could conceivably account for embolic manifestations on both sides of the circulation.

It appears that until four or five weeks before the patient consulted her physician, the symptoms were those of a gradually diminishing cardiac reserve. Then she developed an aching pain in the left upper arm; constantly present, but worse on effort—presumably, effort involving the arm—and lasting four weeks, at the end of which time there was a severe exacerbation of the pain. There is no further mention of this pain, and the only clue we have regarding it is the statement that "the pulse seemed stronger in the right arm than in the left." In view of subsequent events, it is fair to assume that the symptom was due to an embolus to the left arm that impaired the circulation sufficiently to cause pain but did not endanger the nourishment of the tissues because of the free anastomotic circulation in the arm. The exacerbation of the pain was probably due to propagation

of a thrombus proximal to the embolism; such propagation often occurs. Next, the patient developed numbness and coldness in the right leg, the latter being confirmed on physical examination, and pulsations of the dorsalis pedis artery could not be felt in the right foot. Here again, the circulation to an extremity was impaired, I believe, by an embolus, but not sufficiently to necessitate or warrant any drastic measures to save the affected part. These two emboli found their way into the peripheral circulation by way of the left side of the heart, and of necessity came from either the pulmonary veins or the chambers of the heart itself. Assuming that the septal tissues were intact, the most likely source was from an auricular thrombus.

After about two weeks, the patient developed a sudden sharp pain over the left chest, with respiratory embarrassment, and in the course of time was found to have signs of consolidation in the left lower lung. I should interpret this episode as one of pulmonary infarction from an embolus. With pain in the left leg and tenderness in the right calf and over both saphenous veins, thrombophlebitis in the deep and superficial veins of the lower extremities seems a likely source of such an embolus. In the presence of any sort of septal defect, venous thrombosis in the extremities might, in fact, account for all the embolic manifestations in this patient, but I do not believe such a defect was present here.

The terminal symptoms included unlocalized abdominal pain, sudden extreme dyspnea, pallor and cyanosis. The abdominal pain may very well have been the result of the migration or propagation of a large thrombus from either extremity or from the pelvic veins. The sudden dyspnea and circulatory collapse, from which the patient died, I should interpret as due to massive pulmonary infarction from an embolus arising in the deep venous circulation.

If I am correct in my analysis of this case, post-mortem examination should reveal: rheumatic heart disease, myocardial hypertrophy, mitral stenosis and regurgitation, possibly slight aortic stenosis, evidence of mural thrombi in the left auricle, thrombophlebitis of the deep and possibly the superficial veins of the lower extremities,—with a free or propagating thrombus in the larger venous radicles,—multiple pulmonary infarcts and evidence of peripheral embolism to the right leg and left arm.

DR. PAUL D. WHITE: I should like to ask Dr. Glendy if he thinks the engorgement of the neck veins noted on first examination and the changes in T waves might be due to a dilatation of the right ventricle, not wholly from failure but perhaps

from a previous episode of pulmonary embolism.

DR. GLENDY: I think that is true. All we have to go on so far as previous pulmonary infarction is concerned is the condition of the lungs reported on the first examination and said to be essentially normal. Of course, I suppose it is possible to have pulmonary infarction of sufficient degree to produce such a picture, but it does not seem likely in view of the fact that the lungs were reported normal.

DR. WHITE: It would help to explain the electrocardiogram.

DR. GLENDY: Yes.

#### CLINICAL DIAGNOSES

Rheumatic heart disease.  
Mitral stenosis and insufficiency.  
Slight aortic stenosis.  
Auricular fibrillation.  
Coronary insufficiency?  
Embolus, right leg.  
Phlebitis.  
Pulmonary infarct.

#### DR. GLENDY'S DIAGNOSES

Rheumatic heart disease.  
Myocardial hypertrophy.  
Mitral stenosis and regurgitation.  
Slight aortic stenosis?  
Mural thrombi, left auricle.  
Thrombophlebitis, lower extremities.  
Multiple pulmonary infarcts.  
Embolism, right leg and left arm.

#### ANATOMICAL DIAGNOSES

Coronary thrombosis.  
Infarction of heart, old and recent.  
Endocarditis, chronic, rheumatic, with mitral stenosis (severe) and aortic stenosis (slight).  
Pulmonary embolism.  
Pulmonary infarction.  
Pleural effusion, left.  
Thrombosis, popliteal veins, bilateral.  
Embolism, popliteal artery, right.  
Infarct of kidney, right.

#### PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: Post-mortem examination bore out most of Dr. Glendy's predictions. It showed a little more as well. There was an old rheumatic heart disease, with a fairly severe mitral stenosis and also involvement of the aortic valve, although not enough, I should think, to be functionally significant. There was also severe coronary sclerosis, with diffuse atherosclerotic narrowing of all the branches and a fairly recent thrombosis in the right coronary artery. Consequent to

this was a focus of infarction in the posterior wall of the left ventricle, with an overlying thrombus. There was no thrombus in the auricle. The embolus was found in the right popliteal artery. Unfortunately, the left brachial artery was not examined, so that we cannot say whether there was or was not an embolus. Almost certainly, the source of the emboli was the thrombus overlying the cardiac infarct.

DR. WHITE: The thrombus in the coronary artery could not have been embolus?

DR. MALLORY: I do not believe so. It overlay an atheromatous plaque, and looked like a perfectly good thrombus of fairly recent origin. There was a small infarct in the kidney as another manifestation of embolism. Thrombophlebitis was found in the deep veins of the calf on both sides, more marked on the left than on the right. Pulmonary emboli were present. One of these had evidently occurred many days; perhaps a couple of weeks, before death and had produced a rather large single infarct of the left lower lobe. This embolus was rather firmly adherent in the branch of the pulmonary artery, and the infarct showed early signs of organization at the periphery. There had also been a shower of smaller emboli to other pulmonary vessels, particularly in the right lung, none very large, and all out in the periphery; all of them were very recent, none caused infarction, and none were adherent. That, I imagine, represents the terminal episode.

DR. WHITE: The earlier infarct might have been there prior to two weeks.

DR. MALLORY: About two weeks would be my guess on that.

DR. WHITE: After the patient was examined the first time?

DR. MALLORY: Yes; there was an episode of pleural pain at about the right time.

DR. GLENDY: What about the explanation of the phlebitis? Was there any propagation in the pelvis?

DR. MALLORY: We found nothing above the popliteal veins. One thing of a little interest was a left hydrothorax of 3500 cc.—a very large amount of pleural fluid. Usually, when unilateral hydrothorax is present, it is on the right, but in this case the right pleural cavity was dry. Small pleural effusions do occur secondary to infarction, but we have never seen a pleural effusion approaching the size of this one that we should heretofore have attributed to infarction.

DR. WHITE: Did you state the age of the myocardial infarct?

DR. MALLORY: The sections show both old scarring and fairly fresh necrosis. I cannot estimate its age with any accuracy.

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established in 1828

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND  
PUBLISHED UNDER THE JURISDICTION OF THE  
COMMITTEE ON PUBLICATIONS

Official Organ of

THE MASSACHUSETTS MEDICAL SOCIETY  
and

THE NEW HAMPSHIRE MEDICAL SOCIETY

## EDITORIAL BOARD

Joseph Garland, M.D.	Stephen Rushmore, M.D.
William B. Breed, M.D.	Henry R. Viets, M.D.
George R. Minor, M.D.	Robert M. Green, M.D.
Frank H. Lacey, M.D.	Charles C. Lund, M.D.
Sheldon Warren, M.D.	John F. Fulton, M.D.
George L. Tobey, Jr., M.D.	A. Warren Stearns, M.D.
C. Guy Lane, M.D.	Dwight O. Hara, M.D.
William A. Rogers, M.D.	Chester S. Keeler, M.D.

## ASSOCIATE EDITORS

Thomas H. Linsman, M.D.	Donald Munro, M.D.
Henry Jackson, Jr., M.D.	

Walter P. Bowers, M.D., EDITOR EMERITUS

Robert N. Nye, M.D., MANAGING EDITOR

Clara D. Davies, ASSISTANT EDITOR

**SUBSCRIPTION TERMS:** \$6.00 per year in advance, postage paid, for the United States (medical students, \$3.50 per year); Canada, \$7.04 per year, Boston funds \$5.52 per year for all foreign countries belonging to the Postal Union.

Material for early publication should be received not later than noon on Friday.

The Journal does not hold itself responsible for statements made by any contributor.

Communications should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston, Massachusetts.

## PROCUREMENT AND ASSIGNMENT SERVICE

The enrollment forms and the questionnaires for the Procurement and Assignment Service have been or are about to be forwarded to every registered physician in the United States. The need for medical officers in the armed services is acute, and at the same time medical services to other governmental agencies, industry and civilian communities must be provided or maintained. Hence, all physicians, regardless of age, sex, race, physical condition, citizenship or employment, and regardless of any enrollment forms or questionnaires that have previously been made out, should carefully fill out these forms and **IMMEDIATELY** return them in the envelopes that are enclosed, which require no postage. Only with

the information that will be obtained from these forms by the National Roster of Scientific and Specialized Personnel, which will be made available to the Procurement and Assignment Service, can the latter intelligently and expeditely perform its functions, which are so vital to the war effort.

## "HOLD FAST THAT WHICH IS GOOD"

A EUROPE in ruins laments the wanton destruction of the physical monuments of its civilization. Cathedrals are reduced to rubble; art galleries are destroyed, and their treasures of painting and sculpture burned, broken or ravished; schools, hospitals, reservoirs, railways, all the implements of civilization are scattered upon the blasted earth, whose peoples succor their wounded and lament their dead. And all because a paranoiac person with a messianic megalomania has indoctrinated a part of a great nation with a passion for the satisfaction, by ruthless force, of spurious grievances, and has cowed the rest into subservient support of his infamous ambitions.

Libraries have not escaped this holocaust. Louvain, barely rebuilt since the *furor Teutonicus* razed it, has again been leveled. The Royal College of Surgeons is in ruins—its priceless literary treasures, its collections prepared by the very hands of John Hunter, its medical memorabilia blown to bits. The University of Paris has been robbed for the enrichment of the seats of spurious learning of the self-styled Nordic superman, whose servile sycophantic scholars pervert and falsify the accepted facts of history and science to give plausibility to his monstrous ideology.

We in America, so remote geographically from the lair of this Caliban of civilization on the East and from his infamous imitators to the West, cannot believe that our homes and treasure houses are in real danger of physical destruction. Perhaps we are right; or perhaps we have learned nothing from Pearl Harbor and Bataan. Be that as it may, there are other dangers, insidious but fatal. A library may be demolished by a bomb, or it may suffer slow and deadly decay from neglect. We are bringing all our resources—mental, physical and



financial — to the winning of a free way of life for the peoples of the earth. It would be folly to lose through indifference the fruits of years of patient effort. Such fruits are perishable; they cannot be left unwatered for the duration of the national emergency with the expectation that they will be found sound and nourishing afterward.

Such an institution is the Boston Medical Library, whose present situation and prospects are described in the annual report of its president elsewhere in this issue of the *Journal*. It deserves and should receive, in some form or other, the support of every reputable physician in Boston — or, rather, in New England. Those who are fellows should not withdraw unless forced to by dire necessity; those who are not should seek fellowship. All should encourage it by entering its house to enjoy its privileges and by spreading abroad its good report. The purpose of its custodians has not changed since Dr. Chadwick, some sixty-four years ago, in the third year of its existence, wrote the first request for funds: "With this record of past achievements, the Association now appeals for aid to meet its present wants, and to provide for its immediate entrance into a wider sphere of prosperity and usefulness."

---

## TYPHOID CARRIERS

THE day is past when typhoid fever is being spread in large epidemics by water and milk. Safeguards now thrown around such supplies eliminate the possibility of large epidemics, and small ones are becoming exceedingly rare. Although, since 1915, the disease has decreased in Massachusetts from the level of over 2000 cases a year to less than 100 a year, there is no expectation that it can be completely eliminated, because numerous sources of infection are still present.

It is a well-established fact that more than 3 per cent of the persons who contract typhoid fever continue to harbor typhoid bacilli during the remainder of their lives, usually in the gallbladder but sometimes in other foci. In the years when the prevalence of typhoid fever was high, facilities to detect convalescent carriers by proper laboratory

supervision of recovered cases were not available. Consequently, many of those who had the disease in the past now harbor virulent typhoid bacilli in their intestinal tracts and many of the typhoid cases of the present day are due to contacts with such persons. From time to time, estimates have been hazarded regarding the number of typhoid carriers now present in Massachusetts. These estimates have varied within considerable limits, but there are probably at least 1500 such carriers in the State today. Only one tenth of these cases are on the records of the Department of Public Health, and most of these were discovered in the investigation of reported cases.

It is therefore not surprising that occasional incidents such as those described in a paper in this issue of the *Journal* occur from time to time. Most physicians are familiar with the fact that the typhoid bacillus is one of the etiologic agents of cholecystitis. Nevertheless, when a disease is at as low a prevalence as typhoid fever is today, this fact is easily forgotten. In such cases, failure to observe strict precautions may result in the infection of a nurse or a house officer.

From the much publicized story of Typhoid Mary,<sup>1</sup> it is the usual impression that typhoid carriers are very dangerous, causing numerous cases of the disease. Fortunately, in an area where public sanitation and personal hygiene are at as high a level as in New England, it is unusual for such persons to cause cases. Some have gone as long as thirty and forty years without apparently having ever given rise to a single case. The fact that 1500 carriers in Massachusetts are producing only about 75 cases of typhoid fever a year bears out this statement.

So long as typhoid fever continues at its present low rate of prevalence, current cases will produce only a few carriers each year. Furthermore, most of the carriers in the State are persons who had their typhoid fever many years ago and are, consequently, dying off at a high rate. It is therefore to be expected that the disease will drop to even lower levels than those prevailing at present, in

spite of the migration of occasional carriers into the State from areas of higher prevalence.

Physicians treating cases of cholecystitis should make careful inquiry concerning previous typhoid fever. When a past history is elicited, careful laboratory studies should be made to exclude the carrier state. Such preventive measures will dis-close additional carriers and eliminate the chance of infecting contacts in the home and in the hospital.

Recently, the investigation of a case of typhoid fever in a child disclosed the grandmother as the source of infection.<sup>2</sup> The child became ill a few months after the grandmother had been in a hospital where she was under treatment for cholecystitis and cholelithiasis. A careful history at the time of this admission would have disclosed an attack of typhoid fever many years before. Laboratory study would have revealed the carrier condition and prevented a possible death from typhoid fever.

#### REFERENCES

1. Seltz, G. A. The curious career of Typhoid Mary. *Bull. New York Acad. Med.* 15:678-712, 1939.
2. Massachusetts Department of Public Health. Unpublished data

#### MEDICAL EPONYM

##### OPPLER-BOAS BACILLI

These were described by Bruno Oppler, a Berlin gastroenterologist who had been an assistant of Ismar Boas (1858) in the Polyclinic, in the *Deutsche medizinische Wochenschrift* (21:73-75, 1905). The title of the article containing the description is "Zur Kenntniss des Mageninhalts beim Carcinoma ventriculi [On the Recognition of Stomach Contents in Carcinoma Ventriculi]." A portion of the translation follows:

Uncommon as it is to find an entire absence of micro-organisms in the microscopic examination of the stomach contents, it is even rarer that they dominate the field of vision at the expense of all other elements. Leaving yeast and sarcinas for the present out of consideration, up to the present time I have practically found this only in carcinoma. Here there is an apparently quite definite variety of rather slender bacilli, which are grouped in long threads and zigzag lines that so dominate the field that they fill the spaces between the other elements (food particles and so forth) and at times are matted together in thick bundles. Presumably, this is a saprophyte. . . . This luxuriant bacterial growth is particularly seen in carcinomas when the stomach contents show, together with the absence of free hydrochloric acid, the signs of very much di-

minished motility; that is, in those cases in which lactic acid is produced. I have sought for them in vain in the stagnant stomach contents of benign pyloric stenosis or atonic gastrectasis, although, to be sure, these usually contain abundant free hydrochloric acid.

R. W. B.

#### MASSACHUSETTS MEDICAL SOCIETY

##### COMMITTEE ON MATERNAL WELFARE

##### CASE HISTORY: TOXEMIC PREGNANCY FOLLOWED BY UNSUCCESSFUL OPERATIVE DELIVERY AND DEATH

A thirty-four-year-old primipara was sent into the hospital a week before expected labor because of a blood pressure of 130 systolic, 80 diastolic, and a large trace of albumin. She had not been seen during her pregnancy until this date. The past history was essentially irrelevant. The heart and lungs were normal, the uterus was enlarged to a size compatible with term, and the fetal heart was audible. On admission the patient was put to bed and treated medically for this mild toxemia. The blood pressure is said not to have risen any higher, although albuminuria was constant. There was a good deal of swelling in both legs. Six days after entry, labor started spontaneously, and at the end of twelve hours the cervix is said to have been fully dilated. Because of lack of progress, a forceps delivery was attempted but was unsuccessful. Another operator attempted version, which was likewise unsuccessful. By this time, the patient's general condition was poor, and the pulse was rapid, although there is no mention of external bleeding. A consultant was called eight or ten hours later, but the patient died undelivered before his arrival.

*Comment.* This whole case represents atrocious obstetrics. Only the hospitalization and rest in bed for a week before the onset of spontaneous labor are to be commended. It is perfectly possible that the pelvis was not adequate for this particular baby, or that the attempt at forceps delivery failed solely because of the lack of skill on the part of the operator. Had the patient been intelligently observed after the forceps delivery had proved unsuccessful, it would not have been too late to perform an extraperitoneal cesarean section. The unsuccessful attempt at version emphasizes the inadequacy of the medical care. It is possible that in the attempt at version the uterus was ruptured and that death, which occurred several hours after this operation, was due to continued bleeding into the peritoneal cavity.

Such obstetric mismanagement would not occur in any hospital where adequate supervision is routine, and the death was, of course, avoidable.

## WAR ACTIVITIES

### CIVILIAN DEFENSE

#### PLAN TO ESTABLISH BLOOD BANKS

Hospitals in communities exposed to war hazards may receive assistance in the establishment of a blood and plasma bank through funds available to the United States Public Health Service, which will be administered by it through the Medical Division of the United States Office of Civilian Defense. In addition to providing whole blood or liquid plasma for the current needs of hospitals, these blood banks, as well as others already in operation, are to accumulate a reserve supply of plasma for civilian casualties caused by enemy action. Technical and bacteriologic safeguards are to be observed, as recommended by the Subcommittee on Blood Substitutes, Division of Medical Sciences, National Research Council. At the request of the Office of Civilian Defense, a technical handbook on blood and plasma banks has been prepared by this committee, which will be distributed by the Office of Civilian Defense to hospitals.

Following the advice of the committee of the National Research Council, financial and technical assistance will be provided to only three hundred hospitals of 200 or more beds approved by the American College of Surgeons and the Hospital Register of the American Medical Association. These hospitals will agree to maintain required technical standards and to accumulate a surplus of liquid or frozen plasma amounting to one unit per bed within three months. Grants will be made only for the purchase of essential equipment if obtainable locally and for sufficient technical assistance to initiate the project. Hospitals will thereafter be expected to continue to maintain the blood and plasma bank to meet their daily needs as well as the plasma reserve for civilian casualties.

Technical guidance has also been made available through the appointment of Dr. John B. Alsever, of Syracuse, New York, by Surgeon General Parran, of the United States Public Health Service, and his assignment to the Medical Division of the Office of Civilian Defense as technical director of its blood and plasma service. Dr. Alsever will be assisted by regional technical consultants in various parts of the country, whose consulting services will be made available to hospitals in their area.

As a further safeguard for the civilian population, the United States Public Health Service is providing for the production of 50,000 units of dried plasma or human albumin in laboratories approved for the manufacture of biological products by the National Institute of Health. The American Red Cross has agreed to collect the blood for this purpose without interference with its blood-collecting services for the armed forces. This second reserve of dried plasma will be distributed to Office of Civilian Defense depots located in various parts of the country. It will be made available by the Medical Division of the Office of Civilian Defense to stricken communities for their casualties whenever their own local stores of liquid or frozen plasma are in danger of being depleted.

Regional medical officers of the Office of Civilian Defense, who are appointed in the Public Health Service, will be the regional representatives of both agencies for this program. State chiefs of Emergency Medical Service or their deputies may also be appointed consultants or commissioned in the Public Health Service, so that they may act as state representatives for the two agencies in the organization of emergency hospital facilities and the reimbursement of hospitals for the care of civilian casualties. In the more populous coastal states, a full-time state hospital officer may be needed, who will also be eligible for appointment in the Public Health Service.

## MISCELLANY

### NOTES

The sixty-seventh annual reunion and banquet of the alumni of Boston University School of Medicine was held on Thursday, April 23, at the University Club, Boston. Dean Bennett F. A. Avery stated that seventeen members of the staff of the medical school are on active duty with the armed forces and that another is doing research work at the request of the War Department. Dr. Henry M. Pollock, superintendent of the Massachusetts Memorial Hospitals, spoke on the completion of the new Evans Memorial Medical and Research Building, to be opened on May 12. The following officers were elected: Dr. John M. Wilcox, '18, of Woburn, president; Dr. Clifton B. Leech, '19, of Providence, Rhode Island, first vice-president; Dr. Eleanor B. Ferguson, '20, of Boston, second vice-president; Dr. Frank E. Barton, '24, of Boston, secretary; Dr. Kenneth Christophe, '38, of Needham, treasurer; and Dr. Milo C. Greene, '16, of Lynn and Dr. James E. Vance, '23, of Natick, directors for two years.

Boston University School of Medicine has recently received an outright gift of \$10,000 from the W. K. Kellogg Foundation, Battle Creek, Michigan, to be used for student scholarships and loans, with the purpose of assisting in the training of men for military service. The money will be available on July 1, the beginning of the next fiscal year.

## CORRESPONDENCE

### PHYSICIANS FOR THE VETERANS ADMINISTRATION

*To the Editor:* The source of supply of qualified physicians for service with the Veterans Administration has, during the past several months, sustained serious inroads by the needs of the armed forces.

The Procurement and Assignment Service, established by the President, has released to all physicians in the United States a questionnaire to determine the availability of physicians for service with the Government, either in the armed forces or in the civil services. In filling out these questionnaires, physicians may designate their preference for assignment during the present war.

Physicians enter the Medical and Hospital Service of the Veterans Administration in the grade of associate physician, at approximately the same pay as a first lieutenant in the Medical Corps of the United States Army. The volume and variety of the medical activities of the Veterans Administration are approached by few if any other organizations. Abundant clinical material is afforded in all fields of medicine and surgery, except obstetrics and pediatrics. Furthermore, there is ample opportunity for research for those who are interested.

Physicians interested in receiving an appointment should write to the United States Civil Service Commission or to Major Sam F. Seeley, Procurement and Assignment Service, 601 Pennsylvania Avenue, N.W., Washington, D. C., and should also express their preference when completing the questionnaire.

WINTHROP ADAMS, M.D., *Manager*

Veterans Administration  
Bedford, Massachusetts

### TYPHOID FEVER IN HOSPITAL PERSONNEL

*To the Editor:* Because of the occurrence of typhoid fever in hospital personnel, the attached letter was sent to the superintendents of all hospitals and related institutions

in Massachusetts. I suggest that the letter be printed in the columns of the *Journal* for the information of the physicians of the State

PAUL J. JAKMAHL, M.D.  
Commissioner of Public Health

State House  
Boston

#### TO HOSPITAL SUPERINTENDENTS

Cholecystitis may be of typhoid origin. Hospital personnel in charge of gall bladder cases on both medical and surgical wards should constantly keep this point in mind. Recently, a physician in one Boston hospital and a nurse in another contracted typhoid fever because this fact was not taken into consideration\*. The first case was that of a surgical house officer who developed the disease as a result of direct contact with a previously unrecognized typhoid carrier who had just undergone cholecystectomy. The second case was a student nurse who contracted the disease while taking care of a missed case of typhoid fever admitted to the surgical ward as a case of acute cholecystitis.

Exposures to such unrecognized cases of cholecystitis of typhoid origin constitute a real risk to hospital personnel. To avoid such infections it has been recommended that all cases of chronic cholecystitis with a past history of typhoid fever be placed on typhoid precautions until laboratory studies exclude the carrier state. In addition, extreme care should be exercised by those handling dressings and discharges of all other gall bladder cases.

On several occasions in the past, this department has called to the attention of hospital superintendents the occurrence of secondary infection among persons caring for typhoid fever cases before the disease had been definitely diagnosed. It is, therefore, evident that many hospital employees have not been sufficiently protected against typhoid fever by vaccination. Physicians, nurses, laboratory workers and ward attendants are among those requiring antityphoid inoculations.

In addition to the primary series of three subcutaneous inoculations, a single stimulating dose should be administered once a year in order to maintain a sufficiently high level of immunity. This stimulating dose may consist of either 0.5 cc. of the vaccine subcutaneously or 0.1 cc. intradermally.

In the light of present world conditions, it is to be expected that increasingly great responsibilities may come to fall on professional personnel of hospitals. It is important that every possible safeguard be provided for such workers. The proper management of persons with gall bladder disease and those ill with fever of undetermined origin together with antityphoid inoculation of personnel, will reduce considerably the risk of typhoid fever.

PAUL J. JAKMAHL, M.D.  
Commissioner of Public Health

Note: Cholecystitis of typhoid origin (typhoid carrier) is a reportable disease.

\*There were cases as reported and commented on editorially in this issue of the Journal.—Ed.

#### REPORT OF MEETING

##### BOSTON ORTHOPEDIC CLUB

A regular meeting of the Boston Orthopedic Club was held at the Boston Medical Library on December 15, with Dr. Otto J. Hermann presiding. The speaker of the

evening was Dr. John Scudder, of New York City, who discussed 'Shock'.

Studies on the ionic changes during this condition, particularly in regard to potassium, originated in the work of the botanist, Osterhout, and have been carried on by Dr. Scudder after the manner of Dr. James L. Gamble. Allusion was made to the increased action current by an elevation of the potassium content of a system and its return to normal when sodium is introduced. The close analogy of sea water, plasma and interstitial fluid brought out by Dr. Gamble was contrasted to the great difference in cellular fluid. The deleterious effect of the potassium ion on the electrocardiogram of the cat and the saving effect of sodium or adrenocortical extract were pointed out.

Several varieties of experimental shock were shown to have the common factor of a change in the potassium ion content. Noxious stimuli are known to increase shock, which is a principle behind the deflation of intestinal obstruction. Distention of a balloon in the intestinal tract of a cat not only increases the specific gravity of the blood but also causes an elevation of the potassium content. These values return to normal only if the distention is relieved in less than thirty-six hours, but not if the condition persists over forty-eight hours. This, of course, is an important consideration in the treatment of shock. Esophageal obstruction is as fatal in the cat as that at the duodenum, with an elevation of the specific gravity of the blood thirty-six hours before any ionic changes occur. Similar electrolyte changes occur in acute pancreatitis and hemorrhage, but are measurable only late in the syndrome. The protein values change but little. The terminal outpouring of the potassium ion from the tissues occurs after all other materials have been exhausted. In experimental shock produced by trauma, there is an elevation of serum potassium that is relieved by the administration of sodium. Therefore, one variable of all types of shock appears to be an alteration of all the body fluids as well as plasma, such as the cerebrospinal, pericardial, peritoneal, lymph and tissue fluids.

Cases of shock of various sorts in human beings were cited. In a case of ruptured kidney, an early and rapid rise of serum potassium only gradually assumed normal levels. Early operations in such cases are contraindicated, therefore, and should be postponed until normal kidney function has been restored. In a case of an untreated burn, there was absorption of material from cellular breakdown causing an elevation of the potassium ion, with gradual resumption of normal levels in this strong patient. But such a recovery might not occur in all untreated patients. On the basis of these findings, dehydration therapy for severe head injuries is considered injudicious.

Dr. Scudder emphasized the significance of the electrolyte changes in shock, but pointed out that evidences of hemoconcentration are so far the earliest measurable signs of incipient or early shock. A comparison of venous and capillary blood affords a simple rough method for evaluating this factor, and Dr. Walter B. Cannon showed during World War I that values of 8,000,000 and 5,000,000 red blood cells per cubic millimeter in the capillary and the venous blood, respectively, indicate that irreversible changes have already occurred and that death is inescapable. In determining the degree of hemoconcentration as an indication of shock, Dr. Scudder suggests the use of four determinations: the hematocrit, the specific gravity of whole blood, the specific gravity of plasma and the plasma protein. Any of these alone may be misleading. Anemia may offset dehydration in the hematocrit reading, for example.

The type of therapy should be based on these findings. If hemoconcentration results in an elevation of plasma protein, it is permissible to use parenteral saline infusions prior to transfusion. On the whole, blood is the best therapeutic agent in the treatment of most cases of shock. If blood banks are used, it is essential to withdraw the blood under carbon dioxide to keep the ionic elements in their proper proportions. The use of adrenocortical extracts, as suggested first in World War I, fell into disuse for several years, but has recently been shown in histologic and clinical studies to be of definite benefit in many cases of shock. It has therefore become a useful adjunct to the armamentarium of shock therapy.

As a result of studies on electrophoretic patterns of various blood substitutes, it has been concluded that cellophane bags are not adequate for the storage of plasma. Likewise, frozen plasma has been found more stable than the liquid form. Cohn's albumin is very pure and shows definite possibilities as a blood substitute, but certain caution should be exercised in its use. It calls potassium into the blood stream and builds up the circulating blood volume by withdrawing the intracellular fluids. There is also apt to result an elevation of pulse pressure without a true rise of blood pressure. There is still no complete substitute for blood and sodium chloride in adequate amounts and appropriate proportions. In shock from hemorrhage, physiologic saline solution and adrenocortical extract should be administered first. Then, albumin or blood should be given. If blood banks are to be used, the depots must be very large, as evidenced by the giving of 14 liters of blood in thirty days to a patient with burns.

The discussion was opened by Dr. Walter B. Cannon, who compared some of the simpler early concepts of the mechanism of shock with those of the more recent observers. He asked whether isotonic albumin should be used rather than hypertonic, and also whether the potassium freed during the early stages of shock was enough to cause a fall of blood pressure. It was stated that some observers have not had good results with adrenocortical extract, whereas Katz, in Chicago, believes that desoxycorticosterone acetate may be helpful if given prophylactically. The question was raised concerning the advisability of using plasma alone in burns.

The discussion was continued by Dr. Kenneth Coonse, who emphasized the value of the early diagnosis and proper treatment of shock and minimized the question of potassium ion as a cause or effect of the phenomenon. It was pointed out that the histologic changes observed in the adrenal glands are also demonstrable in other organs and probably are not specific. Other organic extracts might therefore help at the appropriate time, but nothing will be of avail beyond a certain point.

Dr. J. E. Dunphy stressed the need for controlled fluid therapy rather than mere fluids. Potassium is probably not all important or even of primary advantage. Capillary permeability may be caused by the absorption of toxins from sepsis. The prime factor apparently is a discrepancy between the existing vascular bed and the circulating blood volume, and this may be brought about by a number of causes. An increase of the vascular bed may result from nervous impulses such as those following a high spinal anesthesia. Toxins may cause direct injury to the vascular system, and this seems to cause changes in the specific gravity of the blood and plasma protein secondary to the fall of blood pressure. Hematogenic shock, as seen in blood loss, does have initial changes similar to those de-

scribed by Dr. Scudder. Adrenocortical extract has a rational basis and deserves a place in shock treatment, but should not be accepted as a cure-all.

In conclusion, Dr. Scudder emphasized the facts that adrenocortical extract was only one phase of the subject and that its use is absolutely contraindicated in shock from sepsis. One practical observation is that a continued increase of hemoconcentration in the presence of saline infusions indicates the approach of irreversible shock.

## BOOK REVIEWS

*The Autonomic Nervous System: Anatomy, physiology and surgical application.* By James C. White, M.D., and Reginald H. Smithwick, M.D. Second edition. 8°, cloth, 469 pp., with 92 illustrations and 19 tables. New York: The Macmillan Company, 1941. \$6.75.

The first edition of this book, written in 1935 by Dr. White alone, was well received and proved to be a valuable contribution to current medical literature. In six years, much has been added to knowledge of the autonomic nervous system by anatomists, particularly Ranson and Clark, by physiologists, such as Cannon and Fulton, and by surgeons, the two authors of this new edition being important contributors themselves. The book, nearly completely rewritten and vastly improved in its new form, is a fundamental text, invaluable to surgeon, neurologist, cardiologist and many others. The period between editions has given the authors time to revise the old and add the new; the publishers have fully co-operated, and physicians are presented with a complete, up-to-date treatise. The volume, like the first edition, is highly recommended.

*Society and Medical Progress.* By Bernhard J. Stern. 8°, cloth, 264 pp. Princeton, N. J.: Princeton University Press, 1941. \$3.00.

This book was long overdue, and now that it has arrived, students of medical history and sociology will find it a valuable tool in the consideration of problems that directly concern medicine and society. The author, a social scientist of note, brings to the presentation of his material a broad background of intellectual knowledge, a keen understanding of medical problems and a penetrating analysis of the social factors that mold, and in turn are molded by, the advance of medicine. The reader is offered a stimulating review of the steps taken by medicine from its infancy to its present status. The tone of the narrative is heightened by a good account of the role of the medical schools and the development of the modern hospital. The subsequent chapters on urbanization, income and health, conquest of famine, medical advances and social progress and resistances to medical changes give a most graphic picture of the inevitably close relation that now exists between medicine and society.

One is a little disappointed at not finding reference to Zabdiel Boylston or W. T. G. Morton. Furthermore, to find on page 182 that the Warburton anatomical act of 1832 is referred to as the first of a series of laws in this connection is to overlook the fact that Massachusetts passed the first anatomical act in 1831. These points, however, are indeed minor.

A feature worthy of special note is the excellent bibliography for each chapter that is found at the end of the book. The reviewer is convinced that a book such as this one should be placed in the hands of all readers.

# The New England Journal of Medicine

Copyright 1942 by the Massachusetts Medical Society

VOLUME 226

MAY 7, 1942

NUMBER 19

## A STATISTICAL STUDY OF SIX HUNDRED AND SEVENTY-ONE CASES OF APPENDICEAL PERITONITIS\* (Concluded)

HENRY H. FAXON, M.D.,<sup>†</sup> AND HORATIO ROGERS, M.D.<sup>‡</sup>

BOSTON

### PART II. TWO HUNDRED AND TWENTY-SEVEN CASES WITH PALPABLE MASS ON ADMISSION TO THE HOSPITAL

IN the previous section, dealing with appendiceal peritonitis unassociated with a demonstrable mass, we pointed out the fallacy of attempting a classification on a purely pathological basis, and again we should like to state that it is only by implication or an unjustifiable exhaustive exploration that such a distinction can be made.

The presence of a palpable mass is of major importance in determining the course of treatment and in influencing the prognosis. It is indisputable evidence of a variable degree of localization of the inflammatory process and hence serves to establish a very different clinical entity from those cases in which the possibility of the formation of such a mass is still problematical, and in which it is unjustifiable to assume that such localization will of necessity ever take place.

We have used the term "mass" advisedly throughout this study because a palpable inflammatory tumor is not necessarily synonymous with an "abscess" within the usual meaning of the word. Much confusion has arisen because of the ill-defined usage of the term "appendiceal abscess," which has been employed in certain cases to describe an extensive area of inflammatory fixation about a gangrenous appendix, and in others, a small collection of pus with a negligible number of surrounding adhesions. The term "mass" refers to a tumor of inflammatory origin, of sufficient size

to be demonstrated by palpation, only secondary significance is attached to the fact that such a mass might be constituted in part of a variable amount of frank pus.

The palpation of a mass in the course of physical examination was possible in 154, or 68 per cent, of these 227 cases. In 32, or 14 per cent, the mass was first noted after the administration of an anesthetic, but before the incision had been made. In 32, or 14 per cent, no mass was noted prior to opening of the peritoneal cavity, but at exploration an inflammatory tumor was found that, from its size and location, should presumably have been detected. In the remaining 9 (4 per cent) cases, not only was the mass not felt preoperatively, but even with the abdomen opened, it seemed unreasonable to suppose from its relative inaccessibility to external or rectal palpation that it could have been discovered prior to operation.

From this it can be seen that in 82 per cent of these cases the preoperative decision concerning the type of treatment the patient was to receive should have taken into consideration the fact that a mass was present as unmistakable evidence that localization of the infectious process had occurred. It is clear that in many cases the surgeon failed to palpate the abdomen after relaxation had been secured, and before making his incision, and thus embarked on a course of treatment founded on an erroneous conception of the lesion present. It is our opinion that in cases in which a definite mass is first detected after the patient is anesthetized, the question of proceeding with the operation at that time in the light of this new finding should be re-evaluated, for the danger of premature disrup-

\* Inroduction and Part I of this paper appeared in the April 30 issue of the *Journal*.  
Read by title at the annual meeting of the New England Surgical Society, Harvard New Hampshire, September 5 and 6, 1941.  
From the Surgical Services, Massachusetts General Hospital.  
† Assistant in surgery, Harvard Medical School, associate visiting surgeon, Massachusetts General Hospital.  
‡ Chief of surgery, Harvard Medical School, associate visiting surgeon, Massachusetts General Hospital.

tion of a definite but inadequately established walling-off process may far outweigh the danger of a second anesthetic.

In a study that professes to be concerned with the clinical problems presented by patients suffering from appendicitis with an associated mass, it may seem illogical to include the 18 per cent of cases in which the true nature of the lesion was not appreciated before the peritoneal cavity was opened. We believe that the inclusion of these cases is not inconsistent with our conception that the clinical problem of appendiceal peritonitis with mass formation is fundamentally different from that in which no such walling off has taken place, and that these cases differ only in the stage of investigation at which the true status of the disease was appreciated.

The number of patients with appendiceal peritonitis and a mass who were admitted to the hospital annually from 1929 to 1940 has changed but little, and the proportion considered "very ill" on admission has remained relatively constant (Table 1). The annual number of all pa-

TABLE 1. Comparative Incidence of Appendiceal Peritonitis with Mass, together with Proportions and Mortality Rates of the Very Ill Patients.

YEAR	NO. OF CASES	APPENDICEAL PERITONITIS WITH MASS	VERY ILL PATIENTS ON ENTRY	
		%	%	%
1929-1930*	33	7	3	0
1931-1933	69	11	12	25
1934-1936	60	9	22	15
1937-1939	65	10	15	20
Total Averages	227	9.4	14	19

\*It should be noted that this tabulation covers only two years instead of the three-year tabulation of the subsequent periods.

tients admitted to the Massachusetts General Hospital with a diagnosis of acute appendicitis has remained essentially the same. Since there has been a yearly constancy in the number of patients with appendiceal peritonitis in any form, it appears that the incidence of cases that have been permitted to progress to perforation before being referred to the hospital has shown no definite tendency to decrease.

The well-recognized fact that there is a higher incidence of uncomplicated appendicitis in males than in females was likewise true in the cases of appendiceal peritonitis with an associated mass. Almost two thirds (64 per cent) of these cases occurred in males, and this figure so closely approximates the sex ratio (63 per cent males) in our study of cases without palpable mass that one may infer that if acute appendicitis goes on to peritonitis, the sex of the patient is no guide to whether or not clinically demonstrable localization will take

place. The mortality in this series was strikingly higher in males (9.0 per cent) than in females (3.7 per cent), whereas the reverse was true in the cases in which no mass was present.

The well-recognized higher mortality rate in the extremes of life in appendicitis of all types is seen to be especially striking when only patients with appendiceal peritonitis and palpable mass formation are considered (Table 2). Although nearly

TABLE 2. Age Incidence and Mortality.

AGE	NO. OF CASES	AGE INCIDENCE	NO. OF DEATHS	MORTALITY
yr.		%		%
1-15	73	32	7	10
16-50	104	46	1	1
51 and over	50	22	8	16
Totals	227		16	
Average				7.0

half (46 per cent) these cases occurred between the ages of fifteen and fifty years, there was but a single death in this group, whereas in patients under fifteen there was a mortality of 9.6 per cent, and over the age of fifty it reached 16 per cent.

PROGNOSTIC SIGNIFICANCE OF HISTORY

Duration of Illness Before Operation

Operation carried out promptly after the onset of acute appendicitis is attended with a rapid recovery of the patient and a negligible mortality. When symptoms of the disease have been present for over twenty-four hours, the inflammation may either subside spontaneously or progress to involve the peritoneal cavity, and there are no infallible criteria for judging which of these eventualities will take place. The duration of the disease as a factor in the clinical prognosis is of greatest consequence during this indeterminate stage, when the exact nature of the lesion present is largely a matter of conjecture. However, the presence of a mass in the region of the appendix is indisputable evidence of at least a partially successful localization of the inflammation to that area, and the value of our figures regarding the duration of the disease in this series of cases consists largely in providing data from which one can decide when in the course of the condition such a mass can surgically be approached most safely. In certain cases, especially in the very young and the elderly patients, a brief history was suggestive of inaccuracies concerning the recorded time interval of the disease, for a demonstrable inflammatory mass rarely becomes established within forty-eight hours.

To illustrate a significant number of cases for each comparative period, the figures shown in Table 3 have been tabulated at intervals of forty-eight hours. It is apparent, from our experience

in 56 cases, that operation for appendicitis with an associated mass within the first four days of the disease is attended with a low mortality (3.1 per cent). This is in striking contrast to our findings of a 12.5 per cent mortality in patients with ruptured appendix without mass formation operated on within this same period, and emphasizes more dramatically than any of our other comparative figures the fundamental clinical difference between these two groups.

During this relatively early stage of the disease, the mass usually consisted of thickened omentum draped about the appendix, with little or no frank pus. This effective localization of the process, in a form that did not predispose to the spread of infection at the time of operation and made possible an unerring approach through the most favorable incision, provided the chief factor in the low mortality of this group.

In the forty-eight-hour period of the fifth and sixth days of the disease, there was an abrupt and startling rise in the death rate—to 17.4 per cent. From the sixth to the twelfth day of the disease, there was a definite but not unbroken trend to-

this group of patients, and although the number is small, it suggests that the occurrence of chills during the onset of acute appendicitis that goes on to form an inflammatory mass has little prognostic significance. Furthermore, a comparison of this with our other series of cases, in which the incidence of chills was essentially the same (9 per cent), leads us to believe that the occurrence of chills preoperatively is of essentially no help in determining the likelihood that the inflammatory process will extend, in contrast with its manifestation of the signs of localization.

In 1 case, in which incision and drainage without appendectomy were carried out on the twelfth day of the disease, the patient suffered chills postoperatively. The patient ran a septic course following operation and finally died, sixty-two days after drainage, of multiple liver abscesses and pyelophlebitis, confirmed by autopsy.

### Previous Attacks

One quarter (26 per cent) of the patients gave a history of one or more previous attacks, with a mortality somewhat higher for this group (8.3 per cent) than for the cases in which there was no note of an earlier attack (5.9 per cent). It would be misleading to try to draw conclusions from this relatively small difference in mortality rates, but it is of some interest that in the cases of appendiceal peritonitis without mass the apparent influence of previous attacks was favorable rather than unfavorable and that the incidence of cases in which a history of such attacks was recorded was definitely higher (40 per cent).

### Other Factors

In the first series of cases, we showed that when appendiceal peritonitis occurred and no subsequent mass developed, 25 per cent of the histories revealed a sudden episode of increased pain that was interpreted as marking the time of perforation and was of helpful prognostic significance. Only 15 per cent of the cases with a mass, however, gave any clue to when perforation might have taken place, and this fact, when available, was primarily of academic interest, for in all these cases, by the time the patient reached the hospital, localization was an accomplished fact.

A study of the patient's bowel habits immediately preceding and following the onset of symptoms did not bring out any trend of diagnostic or prognostic value. In 22 per cent of the histories, there was some definite note of cathartics, and in these cases the mortality rate (10 per cent) was twice that of the remaining cases (5.6 per cent), in which either no laxatives were mentioned or the specific avoidance of their use was so stated.

TABLE 3. Incidence and Mortality According to Duration of Disease before Operation.

DURATION OF DISEASE AT TIME OF OPERATION days	NO. OF PATIENTS	INCIDENCE		MORTALITY	
		%		%	
1 and 2 .....	18	8		6	
3 and 4 .....	38	17		3	
5 and 6 .....	23	11		17	
7 and 8 .....	38	17		8	
9 and 10 .....	24	11		4	
11 and 12 .....	16	8		17	
13 and over .....	63	28		3	
Total .....	222*				
Average .....				6.7	

\*Four nonfatal cases and 1 fatal case were treated without operation.

ward a lower mortality rate, and after this period the mortality reached essentially the same figure (3.2 per cent) that had obtained in the first four days of the disease.

It is therefore apparent that when a mass is present, operation done on or before the fourth or after the twelfth day is a relatively safe procedure, with but a 3 per cent mortality. Surgery carried out on the fifth, sixth or seventh day of the illness, however, is especially hazardous, accounting for nearly half (7) the deaths, although only one fifth (21 per cent) of the patients were operated on at that time.

### Chills

In 18, or 8 per cent, of the cases, there was a definite history of chills during the preoperative course of the disease. There was no mortality in



# PROGNOSTIC SIGNIFICANCE OF PHYSICAL EXAMINATION

## Degree of Illness

It has been routine in our hospital records to enter on the physical sheet the examiner's impression of whether the patient was "very ill," "moderately ill" or "not ill." The distinction between the last two groups was so poorly defined in many cases that the patients were grouped together under the single heading of "not very ill." This note is based primarily on the surgeon's intuitive evaluation of the patient's appearance, and it is interesting that in these cases, as well as in those without mass formation, it is the most significant of all the preoperative data.

Table 1 shows that 14 per cent of the patients were very ill on admission, with a mortality rate nearly four times as high (19 per cent) as that for those who were not considered very ill (5 per cent). Well over a third (42 per cent) of the very ill survivors ran stormy convalescences, as contrasted with only one quarter (25 per cent) of the remaining patients. Taken in conjunction with our first series, it is seen that very ill patients were over twice as common (32 per cent) and showed nearly twice the mortality rate (34 per cent) when no mass was present as when a mass existed.

The incidence of very ill children fifteen years or under (25 per cent) was over twice as great as that for patients between the ages of fifteen and fifty (8 per cent), or over that age (12 per cent). This explains in part the high mortality in children, but cannot be advanced as the cause of the even higher rate found in the elderly group.

## Stage of Treatment at Which Mass was Detected

In the 68 per cent of the cases in which the presence of the mass was appreciated before operation and before an anesthetic was administered, the mortality (Table 4) was less than half (5 per cent)

TABLE 4. Incidence and Mortality on Basis of When Mass Was Detected.

MASS DETECTED	NO OF CASES	INCIDENCE %	NO OF DEATHS	MORTALITY %
On physical examination	154	68	7	5
Under anesthesia	32	14	4	13
At operation (should have been felt preoperatively)	31	14	4	13
At operation (could not have been felt preoperatively)	10	4	1	10
Totals	227		16	

that found in the remaining cases (12 per cent). Undoubtedly, the fact that it was possible to palpate without anesthesia an inflammatory tumor in 154 cases means that in this group the process had become better established or was more favorably

located in the right gutter than in the other cases. One would expect the preoperative history to be longer when a mass could be made out on physical examination, and this was borne out by the facts.

In the 14 per cent of the cases in which a mass was first felt under anesthesia, the mortality was 13 per cent. In no case did a surgeon who discovered a mass on the operating table desist from proceeding with surgery, although such a policy has been successfully adopted subsequent to the period covered in this report.

In all the remaining cases (18 per cent), in which the mass was discovered only after the peritoneal cavity had been opened, appendectomy or drainage was carried out at that time with a mortality of 12 per cent. In only 2 such cases did the operator close his original incision and drain the area through a lateral approach; these patients made an uneventful recovery, and we are confident that many of the others would have fared better had similar mental flexibility been shown more frequently.

So far as could be determined from the records, the majority of the masses were located laterally, and detection of the mass and ease of drainage without contamination of the general peritoneal cavity were naturally greatly facilitated.

## Absent Peristalsis

The fact that the infection had progressed to the point where localization was demonstrable as an inflammatory mass suggests that the greater part of the general peritoneal cavity was free of active infection at the time of admission. This relative freedom from widespread infection is confirmed by the fact that in 122 cases peristalsis was stated as being normal in 83 per cent, as contrasted with 26 per cent of the cases without a mass. Whereas, in the latter cases, absence of peristalsis was attended with a mortality of 28 per cent and provided one of the most significant and unfavorable physical signs, in this series of cases it was of little prognostic advantage.

## PROGNOSTIC SIGNIFICANCE OF LABORATORY DATA

The average white-cell count for all patients in this series was 22,000, with a high percentage of polymorphonuclear cells in the relatively small number of cases in which differential counts were done. The pulse rate averaged 114 in the very ill patients and 106 in those who were not very ill. In no case was the admission temperature over 103.5°F., and in nearly one third (30 per cent) it was under 100°F. by mouth. These facts served merely to confirm the preoperative clinical diagnosis, and the prognostic significance of the leukocyte-pulse ratio, on which we laid great

emphasis when considering the patients without mass formation, is meaningless in this series.

#### PROGNOSTIC SIGNIFICANCE OF DIAGNOSTIC ERRORS

The diagnosis in many of the cases in which the mass was not detected preoperatively was "acute appendicitis," and strictly speaking might be considered mistaken. In an indeterminate number of cases, a diagnosis of "appendiceal abscess" was made in which no appendicitis was found, and 1 such patient, in whom the diagnosis was persisted in postoperatively, died of unsuspected carcinoma of the cecum three months following discharge.

Exclusive of these errors, a mistaken diagnosis was made in nearly one tenth (9 per cent) of the cases in this series. Nearly half these (10 cases) were erroneously diagnosed as either benign (3 of ovary) or malignant (2 of cecum, 1 of colon, 1 of kidney, 1 retroperitoneal and 2 unclassified) neoplasms. With these 10 cases, as with 4 others (3 of hernia and 1 of cirrhosis and ascites), it was primarily a misconception of the nature of the mass that was the confusing factor in diagnosis. In 2 of these, the diagnosis of malignant tumor was persisted in even after the peritoneal cavity had been opened, and in both an ileotransverse colostomy was carried out as the initial step of a two-stage procedure. All the patients survived following removal of the appendix (12 cases) or drainage alone (2 cases).

In the remaining 7 cases (3 of pelvic inflammation, 2 of cholecystitis, 1 of enteritis and 1 of nephritis), a misinterpretation of the manifestations of infection gave rise to the diagnostic error. One of these patients died following surgery on the gall bladder, and a second death occurred in a patient with renal infection and diabetes who was moribund on entry and was not considered to have any surgical lesion but in whom an unsuspected appendiceal abscess was discovered at autopsy three days after admission. The other 5 patients all lived following appendectomy (3 cases), drainage (1 case) or spontaneous subsidence of the process without surgery (1 case).

Because of the possibility of revising with relative safety the original intent of the operation after the peritoneal cavity had been opened and the true nature of the lesion determined, the mortality rate for all the above cases (9.5 per cent) was only slightly higher than that in those correctly diagnosed preoperatively (6.8 per cent). This is in striking contrast to the situation found in the cases of appendiceal peritonitis without mass formation, in which an incorrect preoperative diagnosis frequently resulted in treatment that was incompatible with recovery.

#### SUMMARY OF PROGNOSTIC PREOPERATIVE FACTORS

In the patients without a mass, we attempted to estimate the relative prognostic value of certain preoperative findings by citing the contrasting mortality rates occasioned by the presence or absence of a given factor. The same procedure has been followed in Table 5 for this series of cases

TABLE 5. *Relative Prognostic Value of Various Clinical Factors, as Determined by the Mortality Rate Associated with Each Factor, Based on 227 Cases with a Total Mortality of 7.0 Per Cent.*

CLINICAL FACTOR*	MORTALITY WITH FACTOR PRESENT	MORTALITY WITH FACTOR ABSENT
	%	%
Patient very ill on admission	19	5
Patient under fifteen or over fifty years	12	1
Operation on fifth, sixth or seventh day of disease	15	5
Mass not detected on physical examination	12	5
Males	9	4
Cathartics given preoperatively	10	6
Mistaken preoperative diagnosis	10	7

\*In 18 cases with preoperative chills, there were no deaths, but this number is too small to have statistical value

in which the appendiceal peritonitis was associated with a mass. Again, it should be pointed out that this evaluation attempts merely to approximate the true prognostic significance of each factor, for these were found in such varying combinations that the accuracy of their isolated ratings can be only relative.

#### INFLUENCE OF TREATMENT ON MORTALITY RATE

##### Choice of Treatment

*No operation.* In 5 cases, no operation was carried out during the initial hospital admission. In 2 of these, the reason for withholding surgery was a mistaken diagnosis. One was the patient with an original diagnosis of pelvic inflammatory disease who gave increasingly convincing evidence during her hospital stay that the inflammatory mass that gradually subsided without operation was probably of appendiceal origin, and the other was the patient with renal damage who died three days after entry.

Of the 3 unoperated cases correctly diagnosed as appendiceal abscess, the infection in 1 was satisfactorily handled by spontaneous drainage into the rectum. Another patient was discharged against advice, only to be readmitted for an uneventful incision and drainage and subsequent appendectomy; and the third patient, a nine-year-old child whose mass subsided during a hospital stay of seventeen days, returned three weeks later with a recurrence of symptoms that necessitated appendectomy with drainage. The fact that so few pa-

tients were treated without operation lessens the value of the statistical mortality of 20 per cent for this form of treatment.

Because in this series there was only 1 case in which an inflammatory mass subsided without operation, spontaneous drainage or death, we believe that it must be extremely rare in an unoperated case for a localized mass secondary to a ruptured appendix to subside completely without drainage. The persistence of the inciting cause of the infection undoubtedly best explains why conservative treatment is so rarely effective. This is in contrast to the course of an inflammatory mass that develops following appendectomy, for such a process subsided without operation in half those cases in both this and our earlier series in which it was present during the convalescence.

*Immediate operation.* Since a mass was present in all these patients, the first consideration was when surgical attack could most safely be car-

TABLE 6. *Comparative Incidence of Immediate and Deferred Operation and the Operative Mortality of Immediate Operation.*

PERIOD	NO OF CASES OF IMMEDIATE OPERATION	NO OF CASES OF DEFERRED OPERATION	INCIDENCE OF IMMEDIATE OPERATION	OPERATIVE MORTALITY OF IMMEDIATE OPERATION
			%	%
1929-1930*	26	7	79	12
1931-1933	56	13	81	7
1934-1936	32	25	56	7
1937-1939	29	34	46	3†
Totals	143	79		
Averages			64	6.7

\*Note that this tabulation covers only two years instead of the three-year tabulation of the subsequent periods.

†There have been no deaths in the last 44 consecutive cases.

ried out. The urgency of operation found in many of our cases of ruptured appendix without associated masses was not a factor in this series in which the danger of spontaneous spread could be assumed to be practically nonexistent. Every patient about to undergo surgery should receive appropriate preoperative measures to combat existing dehydration, and for that reason we allowed an arbitrary time limit of six hours to carry out such measures; within this period, we still considered that operation was done "immediately." Delay beyond that period in this series of cases implies that we believed that the local process would progress to a stage more favorable to surgery if such delay was instituted.

Whereas during the first five years of this series, four fifths (80 per cent) of the patients were operated on soon after entry (Table 6), this has been true in slightly less than half (49 per cent) the cases during the last five years. This striking change in policy undoubtedly constitutes one of the

factors responsible for the downward trend of the mortality from 12 per cent in the earlier years to 3 per cent more recently.

In 143 cases, immediate operation was carried out, with a mortality of 7 per cent and an uneventful convalescence in 73 per cent of the survivors. In the cases with a history of four days or less operated on within six hours of entry, the mortality was 4 per cent, whereas during the fifth, sixth and seventh days of the disease, there was a mortality of 12 per cent in the cases treated by immediate surgery. Following the seventh day, immediate operation was attended with a 7 per cent mortality.

During the first four days of the disease, immediate operation was carried out more than ten times as often as deferred treatment, and during the fifth, sixth and seventh days, despite a mortality of 11.7 per cent, immediate operation was adopted three times as frequently as conservative observation. Later than the seventh day, the mortality for immediate operation was 7 per cent, and there was a slightly smaller number of cases in which operation was done immediately than in which it was deferred.

*Deferred operation.* In 79 cases, operation was deferred beyond six hours from the time of admission; in over half (54 per cent), the period of observation was under four days, and in the remainder it was over four days, extending as long as twenty-eight days in 1 case. The significant fact about the mortality rate of 5 per cent in all deferred operations is that 3 of the 4 deaths occurred when operation fell on the fifth, sixth or seventh day of the disease, either because an early case had been delayed too long or because a late case not long enough to exclude it from this relatively lethal period. There was no death in the group of 33 cases in which operation was deferred over four days, and there was no case in which it was established that an undrained abscess spontaneously ruptured into the peritoneal cavity.

*Appendectomy versus incision and drainage.* The policy of carrying out appendectomy as a primary procedure in slightly less than half (47 per cent) the cases has remained remarkably constant over the years studied, and the mortality rate for the 104 cases so treated was 8 per cent. It was accepted as a general surgical principle by the members of the staff during the years under consideration that operation should consist of incision and drainage alone, unless it was believed that the appendix could be removed without adding appreciably to the risk of the procedure. It is obvious from a review of the operative notes that there was a disregard of this principle in a considerable

number of cases in which a mistaken sense of pride in securing the appendix at all costs led the surgeon to persist unduly long, or with an unwarranted amount of trauma.

In 10 cases in which no drainage was instituted, the miss made out preoperatively either proved to consist of an indurated portion of the omentum without associated frank pus (8 cases) or was incorrectly taken to represent cancer at the original operation (2 cases). In all save these, cigarette drains were placed in the right gutter or pelvis, depending on the extent of the infection. A special effort was made to bring the drains out along the lateral wall of the peritoneal cavity rather than between loops of small intestine, and when some form of rectus incision was used, drainage through a stab wound was not infrequently (12 cases) employed to accomplish this end.

Incision and drainage alone as the original surgical procedure was carried out in 118 cases, with a mortality of 6 per cent, but always with the expectation that the appendix would be removed at a subsequent operation. Although the number of cases within each group is too small for definite conclusions to be drawn, the statistics (Table 7)

TABLE 7. *Comparative Incidences and Mortalities of Primary Appendectomy and of Incision and Drainage in Relation to Duration of Disease*

DURATION BEFORE OPERATION	NO. OF CASES	INCIDENCE OF PERITONITIS APPENDICITIS*	MORTALITY OF PERITONITIS APPENDICITIS	MORTALITY OF PRIMARY PERITONITIS
		%	%	%
1 to 4	56	73	7	—
5 to 7	46	43	20	13
8 or over	120	37	7	4
Total	222			
Averages		47	7	5.9

\*All the remaining cases had primary incision and drainage.

suggest that the removal of the appendix within the first four days of the disease tends to lower the mortality in a majority of these cases. Furthermore, although removal of the appendix after the fourth day adds materially to the risk, the high mortality rate when operation is done on the fifth, sixth or seventh day of the illness is accounted for not so much by the type of operation that is carried out as by the unfortunate period selected for surgery. In the significantly large number of cases in which operation was performed after the seventh day (120 cases), removal of the appendix as the original procedure nearly doubled the operative mortality, increasing it from 4 to 7 per cent.

#### Technical Factors

**Type of incision** There has been a marked increase in the use of the McBurney incision or one of its modifications at our hospital in recent

years with the belief that the danger of contamination of the general peritoneal cavity is minimized through a lateral approach. The striking finding (Table 8) that the mortality rate was less than

TABLE 8. *Influence on Mortality Rate of Type of Incision at Original Operation*

TYPE OF INCISION	AP. APPENDECTOMY NO. OF CASES	MORTALITY %	INCISION AND DRAINAGE NO. OF CASES	MORTALITY %	TOTAL OPERATIVE MORTALITY %
Right rectus McBurney	89	0	45	11	10
	15	0	73	3	2
Totals	104		118		
Averages		7		5.9	6

one fourth as high when such an approach was used instead of some form of rectus incision seems to substantiate this opinion. We believe, however, that the arbitrary selection of any one incision for all cases is unfortunate, and that the avoidance of unnecessary surgical trauma within the peritoneal cavity in certain cases can best be accomplished through a pirarectus incision, with drainage through a stab wound in the flank.

**Anesthetic** Local anesthesia was rarely used for appendectomy but was deemed the anesthesia of choice for over one quarter (28 per cent) of the patients in whom incision and drainage alone was carried out. Although ether was the agent used in over half (57 per cent) the entire series, there has been a growing tendency in more recent years toward the use of spinal anesthesia if these cases are not suitable for local novocain infiltration. The fact that the mortality rate (13 per cent) was over twice as high when local anesthesia was used as that (5 per cent) when either ether or a spinal anesthetic was employed merely emphasizes the fact that novocain infiltration was employed in a larger percentage of the poor risk cases.

**Chemotherapy** Chemotherapy was available in only the latter part of the period under discussion, and although we are now employing it routinely in patients with appendiceal peritonitis, it was used in but a single case of this series with mass formation.

#### Secondary Operation

There were no fatalities in the 76 explorations done as a secondary procedure following incision and drainage of the peritoneal cavity. In 73 of these, appendectomy was carried out between four and seven months after the first operation, and in the remaining cases, there was an almost even division between those in which the interval was under four months and those in which it was over seven.

In slightly over half (55 per cent) the cases, the secondary operation averaged forty nine minutes,

and it was apparent from a study of the surgeon's notes that the removal of the appendix was technically a relatively simple procedure; in the remaining cases, not including those complicated by such additional surgery as the repair of a hernial defect, the operation was difficult and averaged seventy-four minutes.

We were especially interested in trying to find some correlation between the lapse of time between operations and the relative ease with which secondary appendectomy could be carried out, but could discover no consistent relation between these two factors.

Although we believe that, as a general rule, appendectomy following preliminary incision and drainage should be urged as a secondary procedure to prevent recurrence of further trouble, there were 11 patients in whom, because of advanced age or poor general condition, it seemed wiser to abandon the idea of further surgery. Eight of these patients were over sixty years of age, and of the remaining 3 in their late fifties, 1 was a cardiac and another a diabetic patient. Information is not available concerning the ultimate course of these and the 24 additional patients who failed to carry out our instructions to return for secondary appendectomy.

#### COMPLICATIONS

Complications, excluding an indeterminate degree of peritonitis, which might be considered an inherent part of the original lesion, occurred in over one quarter (28 per cent) of the total series and one third (37 per cent) of the fatal cases. The difference in the incidence of cases with complications following appendectomy (23 per cent) and those with incision and drainage alone (32 per cent) was accounted for by the larger number of incisional hernias found after the latter type of operation.

The ultimate significance of the high incidence of hernias (16 cases) is qualified by the fact that satisfactory repair at the time of secondary appendectomy was effected in 9 out of 13 cases. It is worthy of note that the incidence of these hernias was higher when the McBurney incision was used for simple incision and drainage (12 per cent) than with some form of rectus approach (9 per cent).

Pulmonary disease was encountered postoperatively in 20 patients, in 2 of whom it was a contributing cause of death. The remaining 18 patients survived despite the postoperative clinical findings of atelectasis (13 cases) and pneumonia (5 cases). Although the former did not retard the patient's convalescence, the latter increased by over one week (nine days) the average time required in the hospital.

Major wound sepsis occurred in 10 cases. The average hospital stay of the survivors was lengthened from an anticipated twenty to forty days, but the only death was in a patient who also had a subphrenic abscess. One other nonfatal subdiaphragmatic abscess occurred.

Residual abscesses were noted in 10 cases and, when they did not subside (4 cases) or rupture spontaneously into the rectum (1 case), required secondary drainage by either an abdominal (2 cases) or rectal (2 cases) approach. In 1 of these cases complicated by further chronic sepsis, the patient died after fifty-four days.

The recorded occurrence of fecal fistulas in 11 cases undoubtedly referred in some to the persistent drainage of pus beyond the anticipated time rather than to the presence of a true fistula. In but a single case was it necessary to operate on a patient to correct this condition.

Although the Miller-Abbott tube was not available during the earlier years of this series, there were but 2 cases in which intestinal obstruction requiring corrective surgery developed.

Other complications encountered were phlebitis (3 cases), postoperative hemorrhage (2 cases), parotitis (2 cases), cystitis (1 case) and pylephlebitis with multiple liver abscess (1 case). Although these complications lengthened the hospital stay appreciably, only the patient with pylephlebitis succumbed.

#### *Cause of Death*

In only 1 case with multiple liver abscesses secondary to a pylephlebitis and another with uremia could it be established with any degree of certainty that death had occurred from causes other than a spread of infection in the general peritoneal cavity. The following clinical review of the deaths in this series correlated with the statistical data affords the most constructive approach to a lowering of the mortality rate.

#### PREVENTABILITY OF DEATHS

##### *Errors in Diagnosis*

One patient who was sixty-three years old and very ill might have survived had his infection not been disseminated by operation based on the mistaken diagnosis of cholecystitis.

##### *Incorrect Choice of Treatment*

Although each case must be judged as an individual problem, we wish to point out that in 6 cases the selection of the fifth, sixth or seventh day for surgery seems to us unwise in the light of our experience.

One of these patients was considered very ill on entry, but nevertheless surgery was not deferred and the patient died of general peritonitis and a complicating pneumonia fifteen days after operation. None of the remaining 5 patients were very ill on admission, and yet 3 died of general peritonitis within three days following operation. The remaining 2 survived their first few postoperative days only to succumb at a somewhat later date to prolonged intraperitoneal sepsis.

In 4 of these last patients, primary appendectomy rather than simple incision and drainage was performed, and thus it appears that the operation selected in all but 1 case was of the type that carried nearly twice as high a mortality for this stage of the disease as the alternative form of surgery.

#### *Errors in Technique*

Four patients who were not very ill on admission were operated on at a theoretically favorable period of their disease; yet all of them died of general peritonitis within five days of operation. None of these procedures were unduly protracted, and the implication is that the operative technique was primarily at fault.

#### *Unavoidable Deaths*

One of these 5 patients, previously mentioned as having an appendiceal abscess as an incidental and unsuspected finding at autopsy, entered the hospital in a moribund condition and promptly died of uremia without operation. Another patient had a protracted hospital stay of sixty days and finally died of multiple liver abscesses secondary to pyelephlebitis. The 3 remaining patients fell into the very young or very old age groups. All were very ill on entry, and it would have been difficult to have improved the treatment that was instituted.

So long as the diagnosis of appendicitis continues to be deferred until perforation has taken place, a group of patients will persist whose deaths may be said to be "unavoidable" only so far as the term refers to a condition that has become established as a result of erroneous earlier diagnosis and ill advised treatment.

#### CONCLUSIONS

The following conclusions seem justifiable:

Patients with appendiceal peritonitis with mass formation present a very different clinical entity and therapeutic problem from those found in cases of appendiceal peritonitis without mass formation. The treatment in such cases is surgical.

Operations should rarely be done on the fifth, sixth or seventh day of the disease.

If a policy of deferring operation is adopted, it had best be pursued for at least four days.

The abdomen in all cases of appendiceal peritonitis should be carefully palpated under anesthesia before operation, and if a mass is discovered at that time, the plan of treatment should be reevaluated and operation possibly postponed.

If the presence of a laterally situated mass is not appreciated until after the peritoneal cavity has been opened, any medially placed original incision should be closed and drainage instituted through a McBurney incision.

A McBurney incision or one of its modifications, rather than some form of rectus approach, should be used for both appendectomy and simple incision and drainage, unless the mass lies unusually far toward the midline, when operation through a pararectus incision, with drainage through a laterally placed stab wound, should be considered.

Incision and drainage alone should be done as a primary procedure unless the technical removal of the appendix can be readily accomplished. Observance of this principle is especially important after the fourth day of the disease.

Appendectomy should be carried out within six weeks following incision and drainage unless the patient is in generally poor condition or some complication provides an indication for a longer interval between operations.

Even when a localized mass has formed, the general clinical impression that the patient creates at entry of being very ill or not very ill is of more reliable prognostic significance than any laboratory data.

# RETINAL LIPEMIA AND VISUAL DISTURBANCES ASSOCIATED WITH ACROMEGALY AND DIABETES MELLITUS

## Report of a Case

JOSEPH IGRSHEIMER, M.D.\*

BOSTON

THE following case of acromegaly with diabetes mellitus and retinal lipemia was studied in the Eye Department and also in the Medical Department at the State University in Istanbul, Turkey. It is reported because of its ophthalmologic and endocrinologic interest and because of its clinical bearing on the experimental work in this field.

### CASE REPORT

A 35-year-old man was admitted to the Eye Clinic on April 16, 1939, almost blind. He was over 6 feet tall and was definitely acromegalic. Examination and history pointed to a tumor of the hypophysis. The patient suffered from polyphagia and polyuria; there was complete disappearance of the libido, and x-ray study showed a markedly enlarged sella turcica. Four months previously, he had an illness with fever, and sugar was found in his urine. There was a slight odor of acetone to his breath.

There was a certain amount of exophthalmos in both eyes. Ophthalmoscopic examination showed a definite retinal lipemia, but no other abnormality.

The vision was reduced on both sides to seeing movements of the hands. On the right, a field could not be taken; on the left, in the upper nasal quadrant, a small

fields. However, the findings in the blood and urine remained unchanged.

On May 8, in addition to the insulin, posterior pituitary extract was given parenterally. On May 18, vision on both sides had improved to 5/10 in both eyes. The nasal part of the visual fields was almost normal, a bitemporal hemianopia being present. The sugar content in the urine, however, had not changed. The ophthalmoscopic findings were normal.

On May 20, the insulin was omitted, but the pituitary extract was continued.

On May 31, the patient did not feel well, and the eyes showed a turn for the worse; the vision in the left eye had decreased to 5/20; in the right it was 5/6. The sugar in the urine varied between 2.3 and 3.1 per cent.

On June 3, all medication was discontinued. On June 12, there was a further decrease in vision: 5/10 in the right eye, and 5/35 in the left. The nasal parts of the fields were again somewhat involved. The patient had lost 4 pounds. Two days later, the general condition was worse. Vision on the right was 5/20, and on the left 1/10. Ophthalmoscopic examination showed a return of the lipemia as seen in the beginning. Between June 3 and 13, the sugar in the urine remained unchanged.

On June 13, a course of x-ray treatment was given to the pituitary gland, and on June 25, the general condition was again improved. Vision went up to 5/7 on the right and 5/20 on the left. There was bitemporal hemianopia. On July 11, vision was 5/7 on the right and 5/15 on the left. The fields were unchanged, but the patient could occasionally see some movements in the temporal fields. The lipemic condition in his eyes had again disappeared.

The patient was discharged on July 15. He did not return for further x-ray treatment.

A diagnosis of tumor of the pituitary gland, complicated by diabetes mellitus, was made. There was no increase in the excretion of nitrogenous substances, no ketonuria and no ketonemia. Most remarkable was the increase of total fat and cholesterol in the blood, and in connection with this general hyperlipemia, there existed a very marked retinal lipemia. Besides the retinal change, the patient showed other unusual eye disturbances.

The retinal lipemia in this case was absolutely characteristic. It is not necessary to describe the clinical picture fully, since many descriptions and pictures are available in textbooks and other publications.

### DISCUSSION

It is well known that glycosuria and even severe diabetes, with and without coma, may occur with acromegaly. The relation of the pituitary gland to the carbohydrate metabolism was clarified by clinical studies and the fundamental experimental investigations of Cushing and Davidoff,<sup>1</sup> Houssay

TABLE 1. *Blood Chemical Findings.*

DATE	TOTAL FAT mg./100 cc.	CHOLESTEROL mg./100 cc.	BLOOD SUGAR mg./100 cc.
April 24	6800*	710	390
May 10	6400	630	490
May 27	390	440	370

\*Normal, 500 to 800 mg. per 100 cc.

area of the nasal field still remained. Diastolic pressure in the retinal vessels was 40 mm. of mercury on both sides, with a general blood pressure corresponding to the patient's age.

The sugar and fat content of the blood is shown in Table 1.

There was 3.3 per cent sugar in the urine, but no albumin or acetone.

The basal metabolic rate was normal.

The patient was transferred to the Medical Department on April 22, and 5 days later he was started on insulin (the first 2 days, 40 units; then, 100 units daily) and diet.

By May 5, his general health had improved markedly; his color was much better, and he was cheerful. Vision in the right eye was 1/25, and in the left eye 5/35. There was definite improvement of the nasal part of the visual

\*Associate in ophthalmology, Tufts College Medical School; associate ophthalmic surgeon, Boston City Hospital, formerly in charge of the Eye Department, State University, Istanbul, Turkey.

and Biasotti,<sup>2</sup> Young<sup>3-5</sup> and others. According to the recent studies of Best et al.<sup>6,7</sup> and of Young, there is no pituitary diabetes without involvement of the pancreas. After injection of anterior-lobe extract, with resulting diabetes, an extensive fall in the insulin content of the pancreas and microscopic changes in the islands of Langerhans were noted. One must assume that the pancreatic disease and the lack of pancreatic hormone can be caused by a hypersecretion of pituitary diabetogenic hormone.

The relation of the pituitary gland to fat metabolism is not so clear as that to carbohydrate metabolism. The assertion of Anselmino and Hoffmann<sup>8</sup> and Raab<sup>9</sup> that substances secreted by the pituitary influence the fat metabolism is not yet proved.

Has pituitary diabetes any characteristic features of regular diabetes? Clinically, von Noorden<sup>10</sup> has pointed out that the glycosuria of patients with acromegaly is not influenced so easily by change of diet as the ordinary diabetes is. Alternating hyperglycemia and hypoglycemia in rather sudden changes was seen by Goldschmidt.<sup>11</sup> His case showed acromegalic symptoms and bony destruction of the sella without enlargement; at autopsy, no lesion of the pituitary gland was found even on microscopic examination. According to Joslin et al.,<sup>12</sup> the diabetes found in acromegaly or other pituitary disease does not differ essentially from ordinary diabetes, but it varies from time to time according to the activity of the hypophysis, and as a result a spontaneous temporary or permanent cure of the pituitary diabetes may be effected. Oppenheimer<sup>13</sup> described a patient with coma who after a certain time showed a surprisingly high tolerance for carbohydrates.

The response to insulin seems to be of a certain importance in the differential diagnosis between pituitary and ordinary diabetes. Ulrich<sup>14</sup> pointed out that insulin is less effective in pituitary diabetes and recommended its use to differentiate pituitary from ordinary diabetes. This clinical experience was supported by experimental results.

The retinal lipemia in the case presented in this paper was, in its ophthalmoscopic appearance as well as in its response to insulin, similar to the published cases of retinal lipemia, none of which showed pituitary symptoms. The decrease in blood sugar and blood lipids, however, was much quicker and more marked in most of the published cases. One can say that in the case presented above there was some resistance against insulin, especially so far as the sugar was concerned, and it seems possible that the involvement of the pituitary gland had something to do with this resistance. But it must be said that in McCann's<sup>15</sup> case, which was supposedly due to an ordinary pancreatic disease, the retinal lipemia disappeared

in seven to nine days, whereas both the sugar and the lipids in the blood increased during this time under treatment consisting of 10 to 30 units of insulin a day.

After the insulin was stopped, the patient in the case discussed above became worse in every respect, and retinal lipemia recurred; however, when x-ray therapy was given to the pituitary region, all symptoms improved, and the retinal lipemia disappeared. This indicates that the pituitary lesion was related to the diabetes and especially to the retinal lipemia.

Concerning the visual disturbances, two questions arise. What was the reason for the almost total blindness of this patient? And was the involvement of the nasal fields due to the same source that caused the involvement of the temporal fields?

It would be easier to understand the total blindness if one could assume that the retinal lipemia had, because of impaired nutrition, an injurious effect on the retinal tissue. Reis<sup>16</sup> made such a suggestion, but his case was probably complicated by disease of the optic nerve. There is no doubt that most patients with characteristic lipemia who were tested for visual disturbances had normal function (Turney and Dudgeon,<sup>17</sup> Koellner,<sup>18</sup> Moore,<sup>19</sup> Hardy,<sup>20</sup> McGuire,<sup>21</sup> Wagener,<sup>22</sup> McCann,<sup>15</sup> McKee and Rabinowitch,<sup>23</sup> Chase<sup>24</sup> and Jaffe and Schonfeld<sup>25</sup>).

In some apparently uncomplicated cases, blurred vision or a slight decrease of visual acuity was found (Darling,<sup>26</sup> Rowe<sup>27</sup> and Ferber and Apperman<sup>28</sup>). Only Ferber and Apperman mention that the visual trouble ceased after disappearance of the retinal lipemia. Machlis's<sup>29</sup> patient suffered from diabetic coma with retinal lipemia; when the patient recovered from the coma, he was "virtually blind," but the retinal lipemia subsequently disappeared, with a full return of the visual capacity. This case, complicated by a transient coma, cannot be compared with a case like the one presented above.

It is true that in this case the improvement of the retinal functions was simultaneous with the disappearance of the retinal lipemia and that the decrease of the vision after the insulin was stopped was accompanied by a recurrence of the retinal lipemia. Nevertheless, I cannot believe that the functional disturbance was produced by the lipemic state of the retinal vessels, because in most cases, the lipemia is harmless to the retinal tissue, and it is quite unlikely that in a few exceptional cases the retina could be damaged by lipemia. Furthermore, the effect of x-ray treatment cannot be explained by the assumption that the visual disturbance was caused by retinal disease.



It seems more probable that the effect of both therapeutic agents (insulin and x-ray) was due to their influence on the pituitary-diencephalic region. The pituitary tumor was responsible only for a bitemporal hemianopia, which was very resistant to treatment. Perhaps a second series of x-ray treatments would have brought some results, because after the first there was a slight improvement. It is quite unlikely, however, that the involvement of the nasal visual fields was due to a growing tumor, because in such a case the involvement of the uncrossed chiasma fibers occurs at a relatively late stage, when there is already an optic atrophy. The disks in the patient under discussion were absolutely normal, and the prompt success of the insulin therapy is not in favor of such an assumption.

It is more probable that besides the tumor pressure another process was present in the pituitary-diencephalic region and that this process caused a temporary interruption of the whole optical pathway on both sides. It was influenced by insulin as well as by x-ray therapy, as demonstrated by the improvement of the central and peripheral vision. But the improvement of the peripheral function was seen only on the nasal fields, because the temporal fields (the crossed nerve fibers) were blocked by the tumor pressure. I assume that the tumor hemianopia was superimposed on the other disturbance, which involved nasal and temporal fields at the same time—in other words, that there were two different conditions acting at the same time on the eye apparatus in the chiasmal region. Whether besides the tumor pressure there was an influence on a center in the pituitary gland or somewhere else in the diencephalic region, I do not know. One can be quite sure that the initial improvement, then deterioration and then improvement again were not mere accidents, since the turn for the worse started again as soon as the insulin was omitted.

Some experiences of Zondek<sup>30</sup> and Feigenbaum<sup>31</sup> are notable. The former has drawn attention to a condition that he calls "salt-water obesity." The main symptom is chronic headache, which, according to him, is due to an increase of cranial pressure; he believes that this increased pressure is caused by a retention of water and salts in the cerebral tissue. The localization of this condition in the vicinity of the chiasm could be considered probable by bitemporal hemianopic defects (according to Feigenbaum) that disappeared as did the headache after dehydration therapy and other measures causing the removal of the salts. In Zondek's case, in which the sella turcica was enlarged and there were genital symptoms besides the headaches, the bitemporal hemianopia for colors also disappeared after such thera-

py. This fact showed, according to Zondek, "that not only the pressure of a growing tumor (probably a chromophobe adenoma) caused the changes in the field of vision, but that also processes responsive to therapy, in the vicinity of the tumor, were causative factors."

These observations of Zondek and Feigenbaum and the case reported are different in many respects, but they seem to have one point in common: that pituitary disease may influence the optic pathways not only directly by the pressure of an existing tumor but also in a more indirect way. If this could be confirmed by further observations, it would be interesting from an ophthalmologic as well as from an endocrinologic standpoint.

### SUMMARY

A case of acromegaly complicated by diabetes mellitus with retinal lipemia and peculiar visual disturbances is described and discussed.

636 Beacon Street

### REFERENCES

1. Cushing, H., and Davidoff, L. M. Studies in acromegaly. *Arch. Int. Med.* 39:673-697, 1927.
2. Houssay, B. A., and Biasotti, A. Action diabetogene de diverses hormones hypophysaires. *Compt. rend. Soc. de biol.* 129:1259-1261, 1938.
3. Young, F. G. Permanent experimental diabetes produced by pituitary (anterior lobe) injections. *Lancet* 2:372-374, 1937.
4. Richardson, K. C., and Young, F. G. Histology of diabetes induced in dogs by injection of anterior-pituitary extracts. *Lancet* 1:1098-1101, 1938.
5. Young, F. G. The anterior pituitary gland and diabetes mellitus. *New Eng. J. Med.* 221:635-646, 1939.
6. Best, C. H., Campbell, J., and Haist, R. E. Effect of anterior pituitary extracts on the insulin content of the pancreas. *J. Physiol.* 97:200-206, 1939.
7. Campbell, J., and Best, C. H. Production of diabetes in dogs by anterior-pituitary extracts. *Lancet* 1:1444, 1938.
8. Anselmino, K. J., and Hoffmann, F. Das Fettstoffwechselhormon des Hypophysenvorderlappens; Nachweis, Darstellung und Eigenschaften des Hormons. *Klin. Wchnschr.* 10:2380-2383, 1931. Zur Darstellung des Fettstoffwechselhormons des Hypophysenvorderlappens. *Endokrinologie* 17:1-8, 1936.
9. Raab, W. Die Beeinflussung des Fettstoffwechsels durch Hypophysenstoffe. *Klin. Wchnschr.* 13:281-285, 1934.
10. von Noorden, C. *Die Zuckerkrankheit und ihre Behandlung*. Fourth edition. 367 pp. Berlin: A. Hirschwald, 1907.
11. Goldschmidt, E. Ein Fall von Akromegalie mit Diabetes mellitus, zugleich ein Beitrag zur Physiologie des Hypophysenvorderlappens. *Schweiz. med. Wchnschr.* 65:766-768, 1935.
12. Joslin, E. P., Root, H. F., White, P., and Marble, A. *The Treatment of Diabetes Mellitus*. Sixth Edition. 707 pp. Philadelphia: Lea & Febiger, 1937.
13. Oppenheimer, A. Über das Wesen der Zuckerkrankheit bei Akromegalie. *Klin. Wchnschr.* 9:17-19, 1930.
14. Ulrich, H. The antagonism between insulin and pituitary extract: its demonstration in a patient with acromegaly. *Arch. Int. Med.* 41:875-882, 1928. Insulin in acromegalic diabetes. *Ibid.* 43:785-794, 1929.
15. McCann, W. S. Lipemia retinalis. *Bull. Johns Hopkins Hosp.* 34:302-304, 1923.
16. Reis, W. Zur Kenntniss eines bisher kaum beachteten Augenspiegelbildes bei Lipaemie in Folge schweren Diabetes, nebst Bemerkungen über die pathologische Anatomie der diabetischen Irisepithelveränderungen. *Arch. f. Ophth.* 55:437-468, 1903.
17. Turney, H. G., and Dudgeon, L. S. A case of intraocular lipaemia associated with diabetes. *J. Path. & Bact.* 9:50-58, 1906.
18. Koellner, H. Lipaemia retinalis. *Ztschr. f. Augenh.* 27:411-417, 1912.
19. Moore, R. F. Lipaemia retinalis. *Lancet* 1:366-369, 1915.
20. Hardy, W. F. Lipaemia retinalis. *Arch. Ophth.* 50:543, 1921.
21. McGuire, H. H. Observations in a case of lipemia retinalis. *Am. J. Ophth.* 5:862-865, 1922.
22. Wagener, H. P. Lipemia retinalis: report of three cases. *Am. J. Ophth.* 5:521-525, 1922.
23. McKee, S. H., and Rabinowitch, I. M. Lipaemia retinalis. *Canad. M. A. J.* 25:530-534, 1931.
24. Chase, L. A. Diabetic lipemia retinalis: report of a case. *J. A. M. A.* 97:171, 1931.
25. Jaffe, M., and Schonfeld, W. A. Lipemia retinalis due to diabetes mellitus: with report of case. *Arch. Ophth.* 9:531-537, 1933.
26. Darling, C. G. Retinal lipaemia in severe diabetes. *Arch. Ophth.* 41:355-359, 1912.

7. Kase A H Effect of insulin in treatment of diabetic pemphigus vulgaris *J A M A* 82:1118 1171 1924  
 8. Fisher J and Apperman I Leukemia retinalis diabetes *M J & W* 125 815 817 1927  
 9. Smith S A D Diabetes mellitus complicated by lipemia retinalis and retinoblastoma *J A M A* 83 1428 1924

30. Zondek H On the question of retrocession of Luteal or hemorrhagic under interlary therapy *Acta Ophth Orient* 1 88 91 1939  
 31. Feigenbaum A Certain responsive bitemporal disturbances of the field of vision (excluding those caused by true tumours of the pituitary body) in some endocrine vegetative affectiois *Acta Ophth Orient* 1 78 84 1938

## CLINICAL NOTE

### HAMARTOMA OF THE SPLEEN: REPORT OF A CASE

RICHARD H SWEET, M.D.,\* AND  
SHIELDS WARREN, MD†

BOSTON

A RECENT experience with a case of hamartoma of the spleen, because of the rarity of the condition, prompts us to report this case in some detail.

There are few references to this tumor in the literature, and the standard textbooks of pathology refer to it only briefly. Hamartoma is a tumor composed of tissue, present in excess beyond normal requirements, that can hardly be distinguished from the normal but possesses a limited capacity for aberrant growth. These tumors are benign and clearly demarcated, and often attain a fairly large size. To those of the spleen, the term "splenoma" has been applied. The age of the patient varies. The tumor is probably of congenital or of embryonic-rest origin, and usually attracts attention only by its size. In 6 patients—4 men and 2 women—reported by Mordasini,<sup>1</sup> the ages ranged from twenty-three to eighty-four years. In all, the spleen was enlarged with a clearly demarcated mass or masses that simulated the splenic tissue, but varied in details of histology and arrangement. The only symptoms were those of splenic enlargement. Apparently, the function of the organ was not disturbed. In Fischer's<sup>2</sup> case, that of a forty-two-year-old man with splenic enlargement, the spleen weighed 2100 gm. These tumors have occurred in animals<sup>3</sup> as well as in human beings.

The description and illustration of the histologic findings in this case may help to further the understanding of this rare splenic tumor.

#### CASE REPORT

Mrs. J. F., a 59-year-old Italian-born housewife, was referred to the clinic of the Palmer Memorial Hospital because of swelling of the abdomen. She had been obese as long as she could remember, but stated that since 8 months previously her abdomen had been growing disproportionately

larger. She had consulted a chiropractor first, but failing to obtain relief had gone to her regular physician, who discovered that she had an abdominal tumor. It was also discovered that she had diabetes, she had never taken insulin, however. During the previous 4 months, she had become unusually constipated, having to resort regularly to the taking of laxatives.

The patient had had no serious illnesses and no operations. She had been married for 38 years and had had thirteen children, of whom eight had died in infancy or childhood. She had had four miscarriages. She had had no menstrual periods for several years and had had no vaginal bleeding or discharge.

Physical examination showed a short, obese woman weighing 186 pounds—17 pounds less than she had weighed 6 months previously. The heart appeared normal, except for a soft, blowing systolic murmur over the entire precordium. The blood pressure was 120/80. In the left side of the abdomen was a large, firm tumor mass about 25 cm in diameter. It was easily moved about, but not so freely as many ovarian tumors of that size. Its chief point of attachment was apparently in the upper quadrant rather than in the lower. Bimanual examination of the pelvis revealed a prolapsed but otherwise not abnormal uterus. There was no demonstrable connection between the tumor and any of the pelvic viscera.

Laboratory examinations revealed a red cell count of 3,730,000 with a hemoglobin of 67 per cent, and a white-cell count of 8750 with 76 per cent polymorphonuclears, 16 per cent lymphocytes, 7 per cent large mononuclears and 1 per cent eosinophils. The platelets were normal, and the red cells showed slight poikilocytosis and anisocytosis. The blood sugar was 110 mg, and the cholesterol 141 mg per 100 cc. The blood Hinton reaction was negative, and the urine was essentially normal.

X-ray examination showed a large mass, approximately 17 cm in diameter, in the left side of the abdomen, with its medial border at the lateral psoas margin and its lower border just below the iliac crest. Its outline was relatively smooth.

A preoperative diagnosis of cyst of the spleen was made, and splenectomy was performed on August 2, 1940.

The abdomen was opened through a long, left rectus-splitting incision. The tumor was about the size of a large grapefruit and lay in the substance of the spleen. It felt soft, as though it might be a cyst or perhaps a large hemangioma. It involved the lower but not the upper pole. The vessels of the splenic pedicle, which were very large, were cut between hemostats and tied with a heavy silk ligature. The smaller vessels along the lateral margin and the vasa brevia were tied separately with chromic catgut. There was practically no bleeding during the operation. After it was made certain that the vessels were securely tied, the rest of the abdomen was hastily explored, but nothing abnormal was found except that the gall bladder was distended and contained stones. There was one large stone impacted in the ampulla. Nothing was done about the gall bladder, and the wound was closed in layers in the usual way.

During the first few days, the patient had a moderate elevation of temperature, with a cough and thick yellow sputum due to partial atelectasis at the bases of both lungs.

\*Attending in surgery Harvard Medical School assistant surgeon Palmer Memorial Hospital  
 †Assistant professor of pathology Harvard Medical School pathologist to the Harvard Cancer Commission and to the New England Deaconess and New England Baptist and Fitchburg State hospitals

By the end of a week, this had all subsided, and the convalescence from that time on was completely uneventful. The wound healed well. The patient was discharged on the 16th day after operation.

tissue by a clearly defined capsule. The tissue here was deep brownish red and finely trabeculated, and showed small vessels, as well as ill-defined malpighian follicles. The rest of the spleen was normal in color

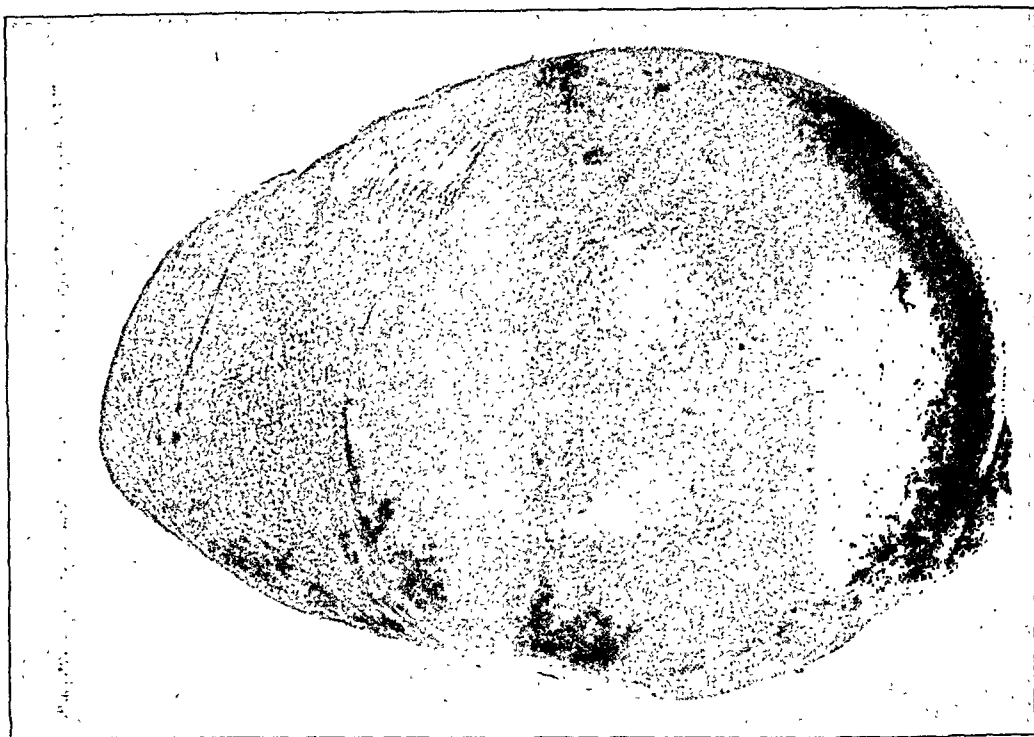


FIGURE 1. *Surface of Spleen, Showing Circumscribed Character of Nodule.*

*Pathological report.* The specimen consisted of a spleen weighing 1120 gm. and measuring 23 by 17 by 7 cm. The surface was smooth, glistening and reddish gray. The lower two thirds was bulbous, with promi-

and showed normal trabeculations and malpighian corpuscles. Microscopically, the splenic tissue proper was not remarkable, although somewhat hyperemic. Within the encapsulated nodule, there was an irregular

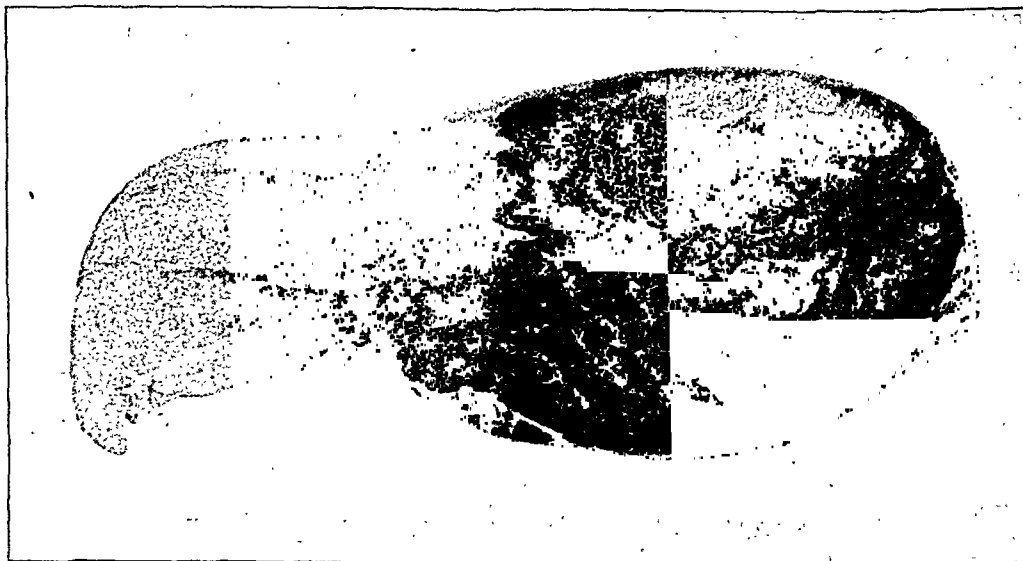


FIGURE 2. *Cross Section of Spleen, Showing Resemblance of Tumor to Splenic Pulp.*

nent capsular veins. The consistence was almost cystic; the tissue at the upper pole was moderately firm. On cut section, the lower two thirds was well demarcated, but not separated from the remaining normal splenic

increase in fibrous stroma and some replacement of the pulp by fibrous tissue. The structure of the sinusoids, trabeculae and malpighian follicles was fairly well maintained. A few plasma cells were present

about some trabeculae. Rare foci of erythropoiesis occurred in the tumor. The hamartoma was not clearly encapsulated, but was of even contour and sharply defined from the normal splenic tissue, and had an incomplete pseudocapsule made up of compressed trabeculae. In the hamartoma, the malpighian corpuscles were present, but ill defined. There were scattered megakaryocytes in the pulp. Many of the sinusoids were fairly heavily congested. Diagnosis: hamartoma of the spleen.

### SUMMARY

A case of splenic tumor due to hamartoma is reported. This is a benign congenital neoplasm reproducing the structure of the spleen.

### REFERENCES

- 1 Mordasini, E. Über Splenome (Hamartome) der Milz. *Virchows Arch. J. path. Anat.* 298 594-615, 1937.
- 2 Fischer, H. Splenomegalie infolge multipler pulpöser Splenome (Hamartoblastoma lienis). *Deutsche Wschr. f. Chir.* 248 552-562, 1937.
- 3 Monari, D. Gli amartomi della milza nel cane (nodi intrasplenicici di tessuto splenico). *Arch. ital. di una e sciol. par.* 3 33-43, 1932.

## MEDICAL PROGRESS

### ENDOCRINOLOGY: TREATMENT OF ABNORMALITIES OF THE ANTERIOR PITUITARY GLAND

JOSEPH C. AUB, M.D.,\* AND DAVID KARNOFSKY, M.D.†

BOSTON

THE anterior pituitary gland, by means of its secretion of tropic hormones, directs growth, regulates the activity of the adrenal cortex and the thyroid gland, stimulates the gonads and leads the ovaries through their complicated cycles, influences carbohydrate and probably protein and fat metabolism and takes on the additional task during pregnancy of influencing mammary development and function. The peripheral endocrine glands, stimulated by the pituitary secretions, form their specific hormones, which not only exert widespread actions but also effect and determine the further activity of the pituitary gland. A dynamic and orderly relation exists, which is not a true equilibrium, since the whole system is continually altering or readjusting itself. This discussion is limited to the treatment of disorders of the anterior pituitary gland that upset its normal relations.

Disorders of hypoactivity result when the pituitary gland diminishes its control over a single or a group of peripheral endocrine glands (as in Simmonds's disease), or when the peripheral gland is diseased, absent or unable to respond regardless of pituitary prodding—as the ovary acts during the menopause. Treatment can be stimulatory by means of specific pituitary hormones if the target gland is capable of responding, or by means of substitutive materials that replace the secretion of the target gland if that organ is not capable of responding. Pituitary hyperactivity may goad the peripheral organs on to renewed and excessive ac-

tivity, as in acromegaly, or the end organs may get out of hand and set up autonomous control, as in primary adrenocortical tumors. Treatment consists of surgery, radiation or the use of hormones or other substances to alter the internal milieu leading to a suppression of the overactive gland or to a possible diminution of the activity of its hormones. The more important materials and methods available for treatment are discussed below.

### AVAILABLE METHODS OF TREATMENT

#### *Pituitary and Related Hormones*

Attempts to make the various fractions of the pituitary gland available for treatment have been extensive, but numerous technical difficulties exist. The gland does not store its secretion in quantities, since its hormones may be elaborated only as needed, and large numbers of glands are necessary to obtain a useful amount of hormone. The number of pituitary hormones that exist is uncertain, but they appear to be numerous. They are probably protein substances, and it is proving very difficult to devise techniques for separating, extracting and purifying them without alteration or loss of potency. Finally, since they have not been characterized chemically, biologic assay is necessary. This is usually involved, expensive and difficult to interpret, and often requires considerable amounts of the hormone to be tested. Also, bioassay is not a certain means of establishing the individual identity of a hormone, since the same substance may give multiple effects. Owing to these impediments, progress has been slow.

Extraction for pituitary secretions is usually done in aqueous, acid or alkaline solutions.<sup>1</sup> The hormones may be precipitated by organic solvents, or by the use of increasing concentrations of salts at

\*Portions of articles in this series are not available for distribution but the articles will be published in book form. The current volume is *Medical Progress Annual*, 1949 (Springfield, Illinois: Charles C. Thomas Company 1941 \$4.00).

†Associate professor of medicine, Harvard Medical School; physician in chief of Collis P. Huntington Memorial Hospital.  
Research fellow in medicine, Harvard Medical School; resident physician, Collis P. Huntington Memorial Hospital.

TABLE 1. *Present Status of Purified Pituitary and Related Hormones*

HORMONE	ACTION	POTENCY OF PURIFIED PREPARATIONS <i>per mg.</i>	CONTAMINATING HORMONES	MOLICULAR WEIGHT	CHARACTERISTICS ON PROTEIN	CHARACTERISTICS ON CARBOHYDRATE	OTHER CHARACTERISTICS
Follicle stimulating hormone (FSH)	Stimulates follicle growth in the ovary and spermatogenesis in the testis	200 <sup>7</sup> to 500 <sup>8</sup> rat units	Slight amount of LH <sup>1</sup>	Not available	Only pituitary hormone in the albumin fraction <sup>1</sup>	15% <sup>3</sup> to 18.7% <sup>6</sup> carbohydrate, probably in amine, amylase will destroy hormonal activity <sup>4</sup> , 1.4% to 8.0% <sup>6</sup> hexosamine	Probably has an -S-S- (disulfide) linkage
Luteinizing hormone (LH) or interstitial cell stimulating hormone (ICSH)	With ICSH causes ovulation and corpus luteum formation, stimulates interstitial tissue of the male and female gonads	200 <sup>7</sup> to 500 <sup>8</sup> rat units	None <sup>2</sup>	About 90,000 in the pig, <sup>9</sup> 40,000 in the sheep <sup>7</sup>	Contains 1.0% tryptophane in the sheep <sup>7</sup> and 3.9% in the pig <sup>10</sup>	2.8% <sup>3</sup> to 4.15% <sup>7</sup> hexose, probably in amine, 2.2% <sup>6</sup> to 3.8% <sup>6</sup> hexosamine	Probably has an -S-S- linkage
Pregnant mare serum (PMS) or equine gonadotropin	Stimulates follicle formation and luteinization	4000 to 7000 rat units <sup>10</sup>	None	Calculated to be 30,000 <sup>11</sup>	Contains tyrosine and tryptophane <sup>11</sup>	11.1% <sup>11</sup> to 17.6% <sup>1</sup> hexose, probably in amine, 8.4% <sup>6</sup> hexosamine <sup>1</sup>	Activity is destroyed if the free amino groups are blocked out <sup>11</sup>
Chorionic hormone of pregnancy urine (APL)	Probably is a luteinizing and interstitial cell stimulating hormone	8000 rat units <sup>12</sup>	None	About 100,000 <sup>12</sup>		10 to 12% hexose, probably in amine <sup>1</sup>	Activity is not destroyed if the free amino groups are blocked out <sup>11</sup>
Lactogenic hormone	Maintains lactation, stimulates the crop gland in the pigeon	10,000 local pigeon units <sup>13</sup>	None	About 26,500 <sup>14</sup>	Contains tyrosine and tryptophane <sup>15</sup>	No carbohydrate	Activity is destroyed if the free amino groups or tyrosine is blocked out
Growth hormone	Maintains growth in hypophysectomized animals	100 hypophysectomized rat units <sup>17</sup>	Slight amount of thyrotropic hormone <sup>1</sup>	Not available	In the albumin fraction <sup>16</sup>	Almost free of sugar <sup>17</sup>	Not inactivated by cysteine, and there is probably no -S-S- linkage <sup>3</sup>
Thyrotropic hormone	Stimulates the thyroid gland	150 chick units <sup>17</sup>	Slight lictogenic, adrenotropic, growth and FSH activities, considerable LH <sup>17</sup>	Not available	In the albumin fraction <sup>16</sup>	3.5% hexose, 2.5% hexosamine <sup>17</sup>	Probably has an -S-S- linkage <sup>17</sup>
Insulin <sup>18</sup>	Lowers blood sugar, exerts antidiabetogenic action	21 international units	None	20,000 to 37,000	Typical protein, amino acid constituents have been almost completely analyzed	None	3.2% sulfur, contains an -S-S- linkage, x-ray diffraction patterns show it to be similar to most proteins

\*The unit of each pituitary hormone, when accurately noted, has an involved definition because conditions of bioassay must be so clearly delineated. It is therefore not possible to present these details here, but one unit is usually the amount that will produce the minimal detectable response in the particular end organ measured in a given species of animal. The test animal used is noted on the chart, but the unit for a given hormone is of no comparative value with that of any of the other hormones.

varying hydrogen ion concentrations. After selective precipitation of each fraction, methods are available to inactivate the contaminating substances, leading to a more homogenous preparation of the desired hormone. This relatively purified material is then bioassayed by numerous technics to determine the amount of the desired hormone and the presence of active hormonal contaminants. Some of the pituitary hormones have been analyzed chemically, and their reactions to different materials studied. They have been examined by electrophoresis and in the ultracentrifuge to determine their homogeneity and molecular weight. By these procedures, the growth, thyrotropic, adrenotropic, lactogenic, follicle-stimulating and luteinizing secretions of the pituitary gland have been isolated and studied. Similar observations have been made on the chorionic hormone of pregnancy urine and on the equine gonadotropin found in pregnant-mare serum. Table 1 shows the present status of these substances. It is of interest to compare these observations to what is known of insulin, a protein hormone that has been available in large quantities in crystalline form for about fifteen years.

There has been some hope that the various pituitary hormones represented prosthetic groups, which were relatively simple, ultimately synthesizable molecules attached to a protein carrier—for example, thyroxine on a globulin. This has not been proved, and the pituitary hormones appear to be individual homogenous proteins. Extraction is difficult, the hormones are not attainable in large quantities, and synthesis appears remote. Unless available sources for these materials improve, as those of the chorionic and equine gonadotropins have, hope for adequate, clinical pituitary therapeutic agents is scant.

Another obstacle in the use of pituitary substances is that they all seem to stimulate in the host the formation of substances referred to as anti-hormones, which neutralize their activity. The literature has been adequately reviewed,<sup>19, 20</sup> and the general opinion formed that antihormones are immune bodies developed against proteins, either those extracted with hormone or the pure exogenous hormone itself. There is at present no evidence that patients injected with and refractory to pituitary hormones inactivate their own secretions.<sup>19</sup> Although it has been observed that the purer the pituitary hormone the less the anti-hormone formation, it is not likely, because of species differences, that the very pure preparations will give no antihormone formation. At least in the luteinizing<sup>7</sup> and lactogenic hormones,<sup>15</sup> species differences in even the most purified preparations have been found. From a practical point of view, three to six weeks after the continued admin-

istration of a pituitary hormone, the antihormone titer gradually increases until the hormonal effect is completely neutralized. When the treatment is stopped, the antihormone titer usually disappears almost as rapidly.<sup>19</sup> Pituitary and related hormones should therefore be given in courses of six to eight weeks, followed by rest periods of similar duration. Gradually increasing amounts during a given course and alternation of the type of pituitary preparation, in both the animal source and the method of extraction, may diminish the antihormone influence and enhance the efficacy of the treatment.

On the market today are various pituitary and related preparations, mostly in an uncertain state of purification.<sup>21</sup> They deteriorate in aqueous solution on standing, and the dried pituitary powders are more satisfactory for storage. All these materials must be given parenterally, and care for specific sensitivity should be observed, particularly with pregnant-mare serum. The preparations available are as follows:

#### *Whole pituitary substance.*

*Growth hormone.* This is impure and of varying potency, and the usual dose is about 1 to 3 cc. daily to three times weekly.

*Lactogenic hormone.* Although fairly pure, the hormone has proved of little clinical value.

*Thyrotropic hormone.* Extracts of this material contain most of the other pituitary hormones, but its thyrotropic activity is usually about 200 chick units per cc. In man, it gives definite effects in responsive thyroid glands, and it is of some value in diagnostic tests in determining the ability of the thyroid gland to respond to pituitary stimulation.<sup>22</sup>

*Gonadotropic hormones.* Purified pituitary gonadotropins are not generally available, but a pituitary extract (called the synergic factor and said to contain mostly gonadotropic hormone<sup>23</sup>), in combination with the chorionic hormone, is reported to give a marked gonadotropic effect. Otherwise, the chorionic hormone is of little value clinically except in the treatment of selected cases of undescended testes.<sup>24</sup> It is available in solutions containing 100 to 500 international units per cc., the usual single dose. Pregnant-mare serum is a potent gonadotropin, but its usefulness is disputed. It is available as a powder and can be made up to solutions containing 500 international units per cc.

Each of these gonadotropins has its peculiar properties, and their proper use is most complicated and not well understood. When they are given sequentially or coincidentally or when estrogens are added, augmentation and modified effects are observed. These hormones may be eminently satisfactory when their technic of use is clarified, and they can be given with some hope of anticipating the result. At present, indications for their use are very limited.

#### *Substitutive Therapy*

In contrast to the rather gloomy pituitary picture are the brilliant successes attending the isola-

tion, purification and in many cases the synthesis of the secretions of the peripheral endocrine organs. Of even greater significance is the discovery of synthetic materials, chemically dissimilar to the hormones but possessing some of their physiologic activities. Today, one may use thyroid, parathyroid, insulin, adrenalin, the various adrenocortical, testicular and ovarian steroids, diethylstilbestrol, methyl-testosterone and dihydrotachysterol to obtain consistent effects that stimulatory treatment will not give. It is impossible to discuss here the extreme ramifications of the use of these substances, except to note that in most cases they are more satisfactory than pituitary hormones, since they are very potent and the dosage can be controlled. They are also relatively inexpensive, and except for parathyroid hormone, produce no significant antihormone effect. The thyroid and some of the steroid hormones, such as testosterone,<sup>27</sup> stimulate the pituitary gland in small doses. Large doses of gonadal hormones, on the other hand, definitely inhibit some of the pituitary activities.<sup>26</sup>

### X-Radiation

X-radiation is extensively used in the treatment of overactivity and tumors of the pituitary gland. In the various functional and obscure disorders, the indications, dosages and dangers are not yet clearly defined. Considerable work must be done on the differential susceptibilities to x-ray of the various pituitary functions at different ages and stages of activity. It is well to remember that pituitary activity is of different significance at different ages. In childhood, it is necessary for growth and for stimulating the target glands to the increased activity essential to normal maturation. In adult life, its usual functions are most manifest in the sex cycles and during the alterations of pregnancy and lactation. After the clinical use of this function continues, but some of the target glands fail to respond to the stimulatory therapy, these relations to age and function are major considerations and, particularly, the treatment of overactivity of the pituitary must not be neglected. If the most sensitive cells are those sensitive to x-ray, this is an important point. Studies of the hormones excreted in the urine after hypophysectomy, similar to observations following the removal of the pituitary gland, have yet to be done. In surgery, it is obvious that all pituitary gland may be destroyed, but the possibility, although unproved, of selectively influencing certain cells. There are favorable reports of pituitary irradiation in

treatment on the pituitary gland, its general use cannot be advocated. The pituitary functions are too vital for the gland to be indiscriminately exposed to irradiation.

On the other hand, in the treatment of hypophyseal tumors, more radical therapy is justifiable, and x-ray therapy appears to be of great value. About 20 to 25 per cent of all intracranial tumors are of pituitary origin. Approximately three quarters of these tumors are of the nonfunctioning chromophobic type and are fairly sensitive to x-rays, except for the cystic type, which makes up about 14 per cent of the chromophobic tumors.<sup>31</sup> Clinically, these two groups cannot be distinguished, but it is commonly agreed that hypophyseal tumors deserve a trial of irradiation before surgery is undertaken.<sup>34</sup> Although there is some question whether this clinical dictum applies in the presence of serious interference with vision, it has been pointed out that x-ray treatment in these cases is often of as much or as little avail as surgery. Since pituitary tumors have such a varied history, the criterion of successful treatment is not so much the prolongation as the enhancement of life—that is, the remission of symptoms and the salvage of sight. In this respect, x-ray therapy is superior to surgery, since it has no operative mortality and less morbidity.<sup>35</sup> If an adequate trial of x-radiation is unsuccessful and there is evidence of progression of the disease, surgery is advised. If surgery is resorted to, the immediate results and prevention of recurrence are considerably improved by postoperative x-ray therapy.<sup>36</sup>

Acidophilic adenomas are small, grow slowly, and compose 20 to 25 per cent of the chromophilic adenomas.

They are usually found in the anterior pituitary gland.

They are usually found in the anterior pituitary gland.

They are usually found in the anterior pituitary gland.

They are usually found in the anterior pituitary gland.

They are usually found in the anterior pituitary gland.

They are usually found in the anterior pituitary gland.

They are usually found in the anterior pituitary gland.

They are usually found in the anterior pituitary gland.

They are usually found in the anterior pituitary gland.

They are usually found in the anterior pituitary gland.

They are usually found in the anterior pituitary gland.

They are usually found in the anterior pituitary gland.

They are usually found in the anterior pituitary gland.

They are usually found in the anterior pituitary gland.

They are usually found in the anterior pituitary gland.

They are usually found in the anterior pituitary gland.

They are usually found in the anterior pituitary gland.

They are usually found in the anterior pituitary gland.

They are usually found in the anterior pituitary gland.

They are usually found in the anterior pituitary gland.

They are usually found in the anterior pituitary gland.

They are usually found in the anterior pituitary gland.

pregnant mare serum (PMS) or equine gonadotropin

Chorionic hormone of pregnancy urine (APL)

Lactogenic hormone

Growth hormone

Thyrotropic hormone

insulin<sup>33</sup>

Probably is a luteinizing and interstitial-cell-stimulating hormone

Maintains lactation; stimulates the crop gland in the pigeon.

Maintains growth in hypophysectomized animals

Stimulates the thyroid gland

Lowers blood sugar; exerts antidiabetic action.

24 international units

100 hypophysectomized rat units

150 chick units

10,000 pig units

10,000 pig units

10,000 pig units

10,000 pig units

10,000 pig units

10,000 pig units

10,000 pig units

10,000 pig units

10,000 pig units

10,000 pig units

10,000 pig units

10,000 pig units

10,000 pig units

hope for adequate agents is scant. in the use of pituitary all seem to stimulate of substances refer to neutralize their action adequately reviewed. Then formed that: developed again with hormone. There patients injected with pituitary hormone inactivation, it is differences, that: no antihormone "zing" and 1

growth and development. The effect of heredity is well known but often not adequately considered. If the patient is found to be large boned, stocky or hirsute, this is perhaps due to heredity and not to the postnatal activity of the endocrine glands. Draper<sup>37</sup> has pointed out the complexity of individual structure and notes that "sex is something more than the mere presence of a gonad." One cannot presume to change the basic stuff of man with hormones. In fact, it appears clear that therapeutic effects from hormones are usually dramatic only when the hormone is needed and that constitutional deviations are not much influenced by their use.

The consequence of environmental, regional, socioeconomic, secular, psychic and medical factors must be understood.<sup>35</sup> For example, the growth of children varies in different regions; children in California are taller than those elsewhere,<sup>33</sup> and great variations appear to be normal in the onset and rate of maturation. Large amounts of data that are essential to help delineate the broad category of normal for each person are being accumulated.<sup>40-42</sup> One must avoid turning a normal child in transition, or a lazy, overindulged person, into an endocrine problem.

#### *Dwarfism*

The evaluation of successful therapy necessarily derives from the accuracy of diagnosis. Dwarfism due to chronic disease or nutritional inadequacy requires treatment of the underlying condition, and it is not yet established whether therapy with endocrine preparations influences the growth of such dwarfs. Cretins and hypothyroid children have definite diagnostic criteria,<sup>43-44</sup> and thyroid stimulates excellent growth so long as the epiphyses of bone are ununited, although the growth factor of the pituitary gland has no effect.<sup>45</sup>

The hypopituitary dwarf (Lorain-Levi type) is delicate, well proportioned and sometimes bright. He has a normal basal metabolic rate, a high sugar tolerance and marked retardation of epiphyseal development, and is neuter in his body configuration and much retarded in sexual development. If possible, treatment should be started early and continued over an extended period. Pituitary growth hormone has been widely used, and although results have been occasionally reported as successful,<sup>46</sup> they are usually variable and inconsistent.<sup>47</sup> The chorionic hormone is probably more useful, apparently inducing a growth response through stimulation of the testes.<sup>48, 49</sup> On the whole, the use of pituitary and pituitarylike hormones to stimulate growth has been a depressing chapter. This may well be due to the quality of hormones available, for the amounts necessary for good effects are large and the antihormones that may develop are very limiting factors. It must be realized,

that growth is a slow process and that prolonged therapy is essential. We have repeatedly tried to stimulate retarded growth by such therapy and the results have never been dramatic and not much in excess of the growth of preceding years. It appears that the pituitary gland has a highly specific growth hormone, and it is unfortunate that its therapeutic effects are not more obvious in this very important problem. As available hormones improve, better results may be obtained, but at the present time, better stimulation of growth can be elicited by the use of peripheral hormones rather than by those derived from the pituitary gland.

The use of testosterone to stimulate growth is still in the experimental stage, but it seems to be the simplest and most effective way. It may act through a stimulatory effect on the pituitary gland,<sup>50</sup> but it also is probable that it has an immediate specific action in causing nitrogen and calcium retention and in inducing muscle growth.<sup>50</sup> It may be given as testosterone propionate, 10 to 25 mg intramuscularly twice weekly,<sup>51</sup> or as methyl testosterone, 10 to 25 mg by mouth daily.<sup>50</sup> The patient should be carefully watched for the occasional undesirable side reactions of the drug, such as hirsutism, macrogenitalism and edema.

Since this treatment is new, several problems must be considered. In striking cases, the appropriate age for starting treatment appears to be early. The hazards of testicular injury, premature closure of the epiphyses and macrogenitalism are more than compensated for by the possibility of removing the patient from the dwarf category. In less obvious dwarfism, it is wiser to delay conservatively because of the striking variations in growth rate that normally develop at puberty. One aid in this decision rests with the skeletal development, which in true pituitary deficiencies is much retarded. So long as the epiphyses are ununited, growth is possible, and the bone age therefore indicates the urgency for treatment. Little growth is to be expected by any therapy after union of the epiphyses. There is some evidence that methyltestosterone is more specific for growth than testosterone propionate,<sup>50</sup> and this suggests the possibility of finding an even more specific growth-stimulating steroid hormone with minimal androgenic activity. The value of simultaneous use of other hormones with testosterone has produced some discussion in the literature. The employment of estrogenic hormones in girls to achieve more physiologic development, the use of simultaneously administered thyroid and the benefit of occasional courses of the chorionic hormone in males to diminish the inhibitory effect of testosterone on the testes must be further studied. The answer to these problems may lead the way to a more promising treatment of pituitary dwarfism.



### *Obesity of Puberty*

The term "Fröhlich's syndrome" to describe the commonly seen obesity of puberty is a misnomer.<sup>52</sup> The patient described by Fröhlich had a tumor at the base of the skull associated with obesity, retarded growth and hypogenitalism. This syndrome is said to be excessively rare: of 140 cases of obesity in puberty reported,<sup>53</sup> not one was a true Fröhlich's. The present tendency is to discard this eponym and divide the obesity problem of puberty into two groups.

It is essential to rule out the very common problem of the fat, overgrown child at puberty. There is often a familial history of obesity, and the condition is equally common in both sexes. The child is often precociously bright and has a smooth, moist skin and obesity of the trunk and mammary glands, with slender extremities. The basal metabolic rate and glucose-tolerance tests are not abnormal, bone development is normal or advanced, and sexual maturity appears at the usual time or earlier.<sup>54-57</sup> These children are often not much concerned about their difficulties and have few subjective complaints, but they are usually overprotected, infantile personalities. This disorder is not regarded as primarily endocrine in nature. It may be due to simple overeating or, as has been theorized, to a functional disorder of the hypothalamus leading to excessive fat deposition. The essential treatment includes diet and psychotherapy, partly of the parents.

The situation in this type of child, however, is not infrequently complicated by a marked retardation of sexual development and sometimes by undescended testes, and the problem then becomes one of a true adiposogenital dystrophy. Such patients may or may not have retardation of bone age and bone growth, a low basal metabolism and a high sugar tolerance. In unpublished work from this laboratory,<sup>58</sup> they all show low excretion rates of the hormones of their sex. Such children represent difficult problems concerning the extensiveness of therapy, for a large percentage of them develop normally later without treatment<sup>59</sup> or may mature promptly with only a reduction of their obesity. Some of them, however, remain sexually underdeveloped and fat, and these represent a serious therapeutic problem.

Treatment should always be dietary, rarely hormonal, because the eventual appearance of sexual maturity is apt to be associated with a spontaneous loss of weight and disappearance of the syndrome. It is not the function of this review to discuss dietetic therapy, but the occasional appearance of hypoglycemia must not be neglected.<sup>60</sup> Aids to diet are amphetamine (Benzedrine) and thyroid. In our experience, thyroid is of considerable help, for

it tends to increase vigor and activity; the suggestion, however, that it may stimulate the appetite out of proportion to its beneficial effects does not conform to our experience. If rapid alteration is indicated, the gonadotropins and testosterone, alone and in combination, have been used with success.<sup>61</sup> A similar type of functional obesity may develop after pregnancy or the menopause.

The second category includes the obese patient with a hypothalamic lesion due to trauma, inflammatory disease, vascular lesions or tumors at the base of the skull or midbrain.<sup>53</sup> The patient may appear similar to those with functional obesity, but in childhood he is usually smaller and has retarded bone development and stigmas of his particular cranial lesion. Treatment obviously consists in combating the etiologic factor, together with dietary and endocrine measures. In all cases of obesity, organic lesions must be carefully ruled out.

### *Anorexia Nervosa*

Increasing attention has been given to anorexia nervosa in recent years.<sup>62-64</sup> Attempts to differentiate anorexia nervosa and Simmonds's disease have been difficult, since it is agreed generally that the starvation regimen of anorexia nervosa leads to a secondary hypopituitarism that ends with a clinical picture almost indistinguishable from that of Simmonds's disease.<sup>65</sup> However, recent work has shown that in anorexia nervosa, although the estrogens fall to a level analogous to that of childhood or Simmonds's disease, the urinary excretion of 17-ketosteroids is not markedly altered.<sup>66</sup> This appears to be an excellent differential technic to establish the diagnosis, since both components fall in Simmonds's disease.<sup>67</sup>

The basis of the therapeutic approach in anorexia nervosa is said to be psychiatric.<sup>68</sup> An analysis of the patient's background and personality, with therapeutic conferences and situational adjustments, may result in the resumption of proper eating. Close attention to the diet is essential, for only high-calorie food should be allowed, and it is occasionally advisable to insist that the patient eat more than is desired. When the appetite returns, the patient may eat astonishing amounts of food and weight gain is rapid, but recovery does not necessarily mean cure, for recurrences are not uncommon. In women, the menses may not return for several years. Younger patients are usually easier to treat, and the longer the illness the more guarded the prognosis. Intercurrent infections are dangerous.

The use of endocrine preparations is of questionable value. Thyroid appears to be detrimental by enhancing the emaciation and thus burning up more tissue. Insulin may be used to stimulate the appetite but, since insulin sensitivity may be pres-

ent, must be given cautiously. Pituitary extracts are ineffective. The use of vitamin supplements, although not specific, is of value.

The production of intermediate degrees of hypopituitarism, by temporary dieting, in people with labile endocrine systems is worthy of note. A patient who four years previously lost 40 pounds in four months by dieting, which she has since regained, but who has remained amenorrheic is a case in point.

### *Simmonds's Disease*

Destructive lesions of the anterior pituitary gland, usually due to surgical procedures, trauma, tumors or granulomas, hemorrhage, diffuse fibrosis or post partum necrosis, occasionally result in Simmonds's disease.<sup>69</sup> Necrosis of the anterior pituitary gland following a difficult puerperium with hemorrhage is the commonest etiology<sup>70</sup> of this very rare disease. In post partum pituitary necrosis, the patient may die promptly, even if vigorously treated, or may develop a chronic hypopituitarism with a low basal metabolic rate, a low blood sugar, amenorrhea, anemia, loss of body hair, apathy, asthenia and precocious senility, and usually cachexia, although this is not an essential feature. Another pregnancy, if possible, permits pituitary regeneration, and the patient may become improved.<sup>76</sup>

Patients with Simmonds's disease run a variable course,<sup>71</sup> termination usually depending on the causative agent or an intercurrent infection, for even complete hypophysectomy is not necessarily fatal.<sup>72</sup> Most of the findings in hypopituitarism are related to atrophy of the endocrine organs maintained by the pituitary gland. Although it is obviously desirable to treat the cause of the pituitary destruction, substitutive therapy for the peripheral glands is usually the only course available. Although these may not be very successful, a program should be carefully worked out and varied for the needs of each patient. Anterior pituitary extract is of no great value, but favorable results have been reported with chorionic hormone.<sup>73</sup> Estrogens and androgens, used separately, may be of help. Adrenocortical insufficiency is often present, and a high-salt diet with desoxycorticosterone is used to combat this condition.<sup>74</sup> Although hypothyroidism exists, thyroid must be given cautiously, since it may accentuate an adrenocortical insufficiency.<sup>75</sup> Hypoglycemia occurs commonly,<sup>76</sup> and frequent feedings may be necessary.

### *Acromegaly*

Acromegaly has a long and progressive course, with spontaneous remissions and exacerbations. Irradiation of the pituitary gland has received much favorable comment recently, and it is said

that it produces relief of some of the troublesome symptoms, such as the severe headaches and eye changes, and some slowing in the progression of permanent changes and the occurrence of complications.<sup>77-78</sup> Exacerbations may necessitate several courses of treatment, and the prognosis is always guarded.

Complications are common. Diabetes mellitus occurs in 17 per cent of the cases on an average of nine years after the onset of acromegaly.<sup>79</sup> Contrary to the usual statements, the diabetes is not more difficult to control than the usual type. Cardiac enlargement and failure develop with surprising frequency in one series, 18 of 24 patients had heart failure.<sup>80</sup> The cause was not clear, but the abnormality responded to the usual treatment. It is well known that macrosplinchina develops in acromegaly, but whether the heart enlarges because of a specific action of the pituitary gland or because of increased work is debatable, and this type of heart disease merits further study. Enlargement of the thyroid gland and elevation of the basal metabolic rate are common. This type of hyperthyroidism is unusual in that response to iodine is not spectacular, thyroid surgery is hazardous, and postoperatively the fall in basal metabolism is not marked.<sup>81</sup> However, if hyperthyroidism is a persistent symptom, subtotal thyroidectomy is advisable, since it may aid or prevent diabetes or heart failure. There have been no recent favorable reports on the use of sex hormones to inhibit pituitary activity in this disease.

### *Cushing's Disease*

Great efforts to distinguish between Cushing's disease (pituitary basophilism) and hyperadrenocorticalism due to primary adrenal neoplasms or hyperplasia are proceeding.<sup>82-84</sup> Attempts to differentiate these two conditions have been rather uncertain because of the pleomorphic character of the syndromes and the intermediate pictures described.<sup>85</sup> This situation is due in large part to the striking differences attributable to the sex and the age of the patient at the onset of the disease. Cushing's disease is regarded as a primary basophilic adenoma of the pituitary gland, which probably exerts its effects by stimulating the adrenal cortex to produce excessive amounts and abnormal types of steroid hormones. This results, in the adult, in the frequently described picture of hirsutism, obesity, painful striae, hypertension, diabetes, osteoporosis, rubicundity and weakness. There is an absence of virilizing effects, and the 17 ketosteroid excretion in the urine is not markedly elevated, in young people bone development may be retarded. These findings may serve to distinguish Cushing's disease from primary hyperadrenocorticalism.

In general, the successes attending the irradiation of the pituitary gland in Cushing's disease

have been only rarely conspicuous. In a recent report from Albright's<sup>86</sup> laboratory, remarkable results have been obtained by the use of testosterone propionate. This was given in 25-mg. doses every other day, and the patients developed immediate nitrogen and phosphorus retention, urinary calcium output decreased, and there were gains in weight and strength. These findings were reversed when treatment was stopped or estrogens were administered. This appears to be a most promising type of treatment on theoretical and practical grounds, and merits extensive trial. In another report, the use of Stilbestrol was reported as beneficial.<sup>87</sup>

### *Gonadal Dysfunction*

It is generally agreed that many gonadal dysfunctions are primarily of pituitary origin, yet it is not the pituitary but the steroid hormones that are being used extensively in these endocrine problems. It would be of extreme advantage, however, to have a more physiologic method of stimulating the ovaries, either to induce the normal sequence of events in the menstrual cycle or to act at a given point in the cycle, such as to induce follicle formation or to cause ovulation in the formed follicles or luteinization of the follicle cysts. The immense literature on this subject was recently reviewed,<sup>88</sup> but the conclusions regarding the pituitary hormones can be simply restated, since results are so discouraging or equivocal. Chorionic hormone alone is of no value.<sup>24, 89</sup> Pregnant-mare serum has been reported to induce ovulation, chiefly by intravenous administration,<sup>90</sup> but this must be a rare phenomenon.<sup>91-93</sup> Purified pituitary gonadotropic substances are just coming into use. It is quite obvious that women do not respond to these substances in a way analogous to the reactions of laboratory animals.

The ovaries of a large group of patients after the injection of various gonadotropic substances, alone and in combination, were studied.<sup>94</sup> The results were variable, and the desired effect was rarely obtained. Ovulation is a delicately controlled mechanism, resulting only from the appropriate balance of hormones present at the propitious moment. The dosage, time, duration, sequence and route of administration and proper combination of hormones must be observed. It is also quite obvious that diseased ovaries will not respond to the same stimulus as normal ones. Attempts to strike the necessary balance are crude as yet, but two therapeutic approaches are suggested. The use of the chorionic hormone in combination with the pituitary synergic principle has been successful in inducing ovulation.<sup>23, 95, 96</sup> The sequential use of pregnant-mare serum (400 to 800 international units daily) for the first ten days of the menstrual cycle, followed by chorionic hor-

mone (500 to 750 international units daily) for the next ten days, is reported to have given a progestational endometrium in 15 of 29 cases.<sup>97</sup> These combined treatments seem worthy of trial in anovulatory cycles. The administration of small stimulating doses of estrogens in combination with the gonadotropins is believed to increase their effectiveness.<sup>88</sup>

### *Cryptorchidism*

The usefulness of the gonadotropic hormones in the treatment of undescended testes has been clearly defined.<sup>98, 99</sup> It is effective only in cases in which no mechanical obstruction to descent exists, and these testes would probably descend at puberty of their own accord. However, in cryptorchidism, a trial with the chorionic hormone is advisable, since the testes may come down, and if not, they are enlarged so that surgery is facilitated. Pseudocryptorchidism must be carefully ruled out. The testes that are lower in the inguinal canal are the likeliest to respond to therapy.

There is some disagreement concerning whether treatment should be started just before puberty or in childhood. The tendency is to start at an early age, since premature closure of the epiphyses or enlargement of the genitalia is not a likely complication of the therapy.<sup>100</sup> The usual course of treatment is 100 to 500 international units of chorionic hormone three to six times weekly for eight or nine weeks. About 20 to 25 per cent of the cases are benefited; the rest should then be treated surgically. The administration of 5 to 10 mg. of testosterone propionate along with the chorionic hormone is said to give improvement in cases in which each hormone has failed when given separately.<sup>101</sup> The disadvantages of using testosterone in children must be considered.

### *Diabetes Mellitus*

The interest in the role of the pituitary gland in diabetes received considerable impetus from Young's discovery that chronic diabetes could be induced in dogs by long-continued injections of anterior pituitary extracts.<sup>102</sup> Insulin, if given along with this extract, or shortly afterward, prevents or cures the diabetes. If the diabetes has existed for several months, insulin has no curative effect. From this was evolved the principle that the pancreas is susceptible to complete exhaustion, but if rested early, it can be revived. It has therefore been suggested that human diabetes be treated early and intensively with a low-carbohydrate, low-calorie diet and insulin, under conditions that tend to rest the pancreas.<sup>103</sup>

The significance of the pituitary gland in the usual type of human diabetes is uncertain. In the hyperpituitarism of acromegaly, it is a late and not

an extremely frequent complication.<sup>79</sup> Although favorable results have been reported,<sup>101</sup> in general the use of estrogens in the treatment of diabetes by suppressing pituitary function has been discouraging.<sup>102, 103</sup> These recent findings, however, have proved most stimulating, and further study is needed of the relation of the pituitary gland to human diabetes.

### Hyperthyroidism

With the well-recognized dependence of the normal thyroid gland on the thyrotropic hormone of the pituitary gland, attempts have been made to attribute Graves's disease, to pituitary overactivity. The hyperthyroidism of acromegaly may be on this basis, but there is no satisfactory evidence that the usual case of Graves's disease has a similar etiology. Occasional and inconstant successes in the treatment of hyperthyroidism have been reported by the use of estrogenic substances<sup>107</sup> and chorionic hormone.<sup>108</sup> These studies, as representing a medical approach to the treatment of hyperthyroidism, are interesting but of no general therapeutic moment as yet.

An unusual subgroup of Graves's disease, referred to as "malignant exophthalmos," is being stressed by Means and his group.<sup>109</sup> In these patients, the exophthalmos is profound, although the basal metabolic rate is only slightly elevated, if at all. This exophthalmos is probably due to large excesses of thyrotropic hormone, which is reported to cause a specific hypertrophy, edema and lymphocytic infiltration of the extraocular muscles.<sup>110</sup> This condition must be carefully differentiated from ordinary exophthalmic goiter, since in the former, thyroidectomy may prove disastrous by increasing the exophthalmos until blindness results. The appropriate treatment, therefore, in the selected case is to attempt to suppress the pituitary overactivity. This consists in the use of nodules and thyroid in a balanced combination to depress the basal metabolic rate and to inhibit pituitary activity. Estrogens are worth trying. If the exophthalmos progresses, x-ray treatment to the pituitary gland and to the orbit may help,<sup>111</sup> and as a last resort, if vision is menaced, orbital decompression may be indicated. If the hyperthyroidism requires treatment, x-ray therapy to the thyroid gland is preferred. Surgery, if used, requires the most considered preoperative and postoperative care.

\* \* \*

To summarize this mass of new work is difficult. It may be stated, however, that the importance of the pituitary gland is fairly well established in many abnormalities of the endocrine glands. Even though it may frequently be the

primary factor, the use of pituitary hormones has, on the whole, been disappointing in therapeutic effects. This is due to the difficulties in obtaining adequate sources and in purification. It is also unwise to use continuous therapy because of the temporary immunity produced by injected pituitary hormones, so that intermittent therapy is imposed. As a result, pituitary deficiencies are now more effectively treated by the use of endocrine hormones derived from the peripheral glands

### REFERENCES

1. Jensen R W and White A. Fractionation of urine extracts of anterior pituitary tissue. *Endocrinology* 26:950, 1940.
2. Jensen J, Tolkdorf S and Rammann F. Purification of the interstitial cell stimulating and follicle stimulating hormones of the pituitary. *J Biol Chem* 135:791, 1940.
3. Fraenkel Conrad J, H. Meyer, H. L. Simpson M F and Evans H M. Further purification of the growth hormone of the anterior pituitary. *Endocrinology* 27:651, 1940.
4. M. Shin W H and Meyer R K. The preparation and properties of pituitary follicle-stimulating fractions made by trypsin digestion. *J Biol Chem* 155:473, 1940.
5. Gurin S. Characteristics of the gonadotropic hormones. *Proc Soc Exper Biol & Med* 49:46, 1942.
6. Evans H M, Fraenkel Conrad J, Simpson M F and Li C H. Characterization of gonadotropic hormones of the hypophysis by their sugar and phosphate content. *Science* 89:249, 1939.
7. Li C H, Simpson M F and Evans H M. Physico-chemical characteristics of the interstitial cell stimulating hormone from sheep pituitary glands. *J Am Chem Soc* 64:367, 1942.
8. Gery P O, Van Dyke H B and Chow B T. Separation in nearly pure form of luteinizing (interstitial cell stimulating) and follicle stimulating (gonadogenic) hormones of the pituitary gland. *J Biol Chem* 131:269, 1940.
9. Sheldrick T, Reichen A, Grier R O, Van Dyke, H B, and Chow B T. The isolation in pure form of the interstitial cell stimulating (luteinizing) hormone of the anterior lobe of the pituitary gland. *Science* 92:178, 1940.
10. Cole H H, Tenkate R I and Goss H M. On the biological properties of highly purified gonadotropin from pregnant mare serum. *Endocrinology* 27:548, 1940.
11. Li C H, Evans H M and Wonder D H. Electrophoretic homogeneity of pregnant mare serum gonadotropin. *J Gen Physiol* 21:33, 1940.
12. Lundgren H P, Gurin S, Bachman C and Wilson D W. The gonadotropic hormone of urine of pregnancy IV. *J Biol Chem* 142:36, 1942.
13. White A, Catchpole H R and Long C N H. A crystalline protein with high lactogenic activity. *Science* 86:87, 1937.
14. Li C H, Lyons W R and Evans H M. Studies on lactogenic hormone. VI—Molecular weight of the pure hormone. *J Biol Chem* 140:43, 1941.
15. Idem. Studies on the pituitary lactogenic hormone. IV. Tyrosine and tryptophan content. *J Biol Chem* 136:709, 1940.
16. Levold H J, Lee M, Hsiao F I, and Cohn, F J. Studies in the physical chemistry of the anterior pituitary hormones: separation of five anterior pituitary hormones into different fractions by use of electric and ammonium sulfate precipitation. *Endocrinology* 26:999, 1940.
17. Fraenkel Conrad J, Fraenkel Conrad H, Simpson M F, and Evans, H M. Purification of the thyrotropic hormone of the anterior pituitary. *J Biol Chem* 135:199, 1940.
18. Jensen H F. *Endocrine Its chemistry and physiology* 252 pp. New York: Commonwealth Fund, 1938.
19. Thompson K W. Antihormones. *Physiol Rev* 21:588, 1941.
20. Thomson D L, Collip, J B, and Selye, H. The antihormones. *J Am J* 116:132, 1941.
21. Freed, S C. Present status of commercial endocrine preparations. *J Am J* 117:1125, 1941.
22. Wilkins I and Fleischmann, W. Hypothyroidism in childhood. *J Clin Endocrinol* 19:108, 1941.
23. Mager, C, and Raveiz F. The effect of combined administration of chronic gonadotropin and the pituitary synergist on the human ovary. *Am J Obst & Gynec* 41:474, 1941.
24. Reports of the Council on Pharmacy and Chemistry the present status of therapy with chorionic gonadotropin. *J Am J* 114:487, 1940.
25. Nathanson I T, and Brues A M. Effect of testosterone propionate upon the mitotic activity of the adrenals in the intact immature female rat. *Endocrinology* 29:397, 1941.
26. Reichenbach N O, and Foltz, L M. A comparative study of the effects of the male and female sex hormones on the pituitary gonadotropic function in women. *Endocrinology* 27:37, 1940.
27. Nathanson, I T, Lee, C, and Meigs, J V. Hormonal studies in artificial menopause produced by roentgen rays. *Am J Obst & Gynec* 40:936, 1940.
28. Huet, J A. Les résultats de dix années de roentgentherapie hypophysaire. *Bull et mens Soc d'électricité radiale de France* 22:20, 1939.

29. Kotz, J., and Parker, E. Treatment of functional disorders of the female by radiation of the pituitary gland. *South. M. J.* 33:832-839, 1940.
30. Pendergrass, E. P., Hodes, P. J., and Griffiths, J. Q., Jr. Irradiation of the pituitary in posterior lobe hyperfunction controlled by biologic tests. *Am. J. Roentgenol.* 46:673-682, 1941.
31. Sosman, M. C. Irradiation in the treatment of pituitary adenomas. *Proceedings Interstate Post Graduate Medical Association of North America*. St. Louis, October 18-22, 1937. Pp. 239-245.
32. Kaplan, I. I. Irradiation of brain tumors at Bellevue Hospital, 1924-1939. *Radiology* 36:588-595, 1941.
33. Schwartz, C. W. Tumors of the hypophysis cerebri from a roentgenologic viewpoint. *Am. J. Roentgenol.* 40:548-570, 1938.
34. Sosman, M. C. The roentgen therapy of pituitary adenomas. *J. A. M. A.* 113:1282-1285, 1939.
35. Schuttker, M. T., Cutler, E. C., Bailey, O. T., and Vaughan, W. W. The chromophobe adenomas of the pituitary: pathologic features and response to irradiation based on a study of 81 verified cases. *Am. J. Roentgenol.* 40:645-659, 1938.
36. Henderson, W. R. The pituitary adenoma: a follow-up study of the surgical results in 338 cases (Dr. Harvey Cushing's series). *Brit. J. Surg.* 26:811-921, 1939.
37. Draper, G. The mosaic of androgyny. *New Eng. J. Med.* 225:393-401, 1941.
38. Meredith, H. V. Stature and weight of children of the United States: with reference to the influence of racial, regional, socioeconomic and secular factors. *Am. J. Dis. Child.* 62:909-932, 1941.
39. Lloyd-Jones, O. California tall children. *Am. J. Dis. Child.* 60:11-21, 1940.
40. Greulich, W. W., Day, J. G., Lachman, S. E., Wolfe, J. B., and Shuttlesworth, F. K. *A Handbook of Methods for the Study of Adolescent Children*. 406 pp. Monographs of the Society for Research in Child Development. Vol. III, No. 2, Serial No. 15. Washington, D. C.: Society for Research in Child Development, National Research Council, 1938.
41. Jung, F. T. The physiologic changes incident to puberty. *Illinois M. J.* 80:477-484, 1941.
42. Nathanson, I. T., Towne, L. E., and Aub, J. C. Normal excretion of sex hormones in childhood. *Endocrinology* 28:851-865, 1941.
43. Wilkins, L., and Fleischmann, W. The diagnosis of hypothyroidism in childhood. *J. A. M. A.* 116:2459-2465, 1941.
44. Shelton, E. K. Hypothyroidism in childhood. *J. A. M. A.* 117:1948-1950, 1941.
45. Beard, E. E. Cretinism: lack of response to anterior pituitary growth principle. *J. Clin. Endocrinol.* 1:293-296, 1941.
46. Schaefer, R. L., and Strickrodt, F. L. Endocrine dwarfism. *Endocrinology* 26:599-604, 1940.
47. Greene, J. A., and Johnston, G. W. Metabolic changes by extracts of anterior hypophysis in primary-pituitary and nonpituitary dwarfs. *J. Clin. Endocrinol.* 1:327-330, 1941.
48. Dorff, G. B. Rapid growth in height produced by chorionic gonadotropin in a dwarfed infantile identical twin. *J. Clin. Endocrinol.* 1:940-944, 1941.
49. *Idem*. Chorionic gonadotropic effects on height and osseous development in sexually underdeveloped young boys. *Endocrinology* 27:403-410, 1940.
50. Wilkins, L., Fleischmann, W., and Howard, J. E. Creatinuria induced by methyl testosterone in the treatment of dwarfed boys and girls. *Bull. Johns Hopkins Hosp.* 69:493-503, 1941.
51. Goldzieher, M. A. Growth and sex hormones. *J. Clin. Endocrinol.* 1:924-927, 1941.
52. Bruch, H. The Fröhlich syndrome: report of the original case. *Am. J. Dis. Child.* 58:1282-1289, 1939.
53. Warnaky, J., Farber, S., Logan, M. L., and Newcomb, A. L. Roundtable discussion of adiposogenital dystrophy. *J. Pediatr.* 19:854-863, 1941.
54. Bruch, H. Obesity in childhood. I. Physical growth and development of obese children. *Am. J. Dis. Child.* 58:457-484, 1939.
55. *Idem*. Obesity in childhood. II. Basal metabolism and serum cholesterol of obese children. *Am. J. Dis. Child.* 58:1001-1022, 1939.
56. *Idem*. Obesity in childhood. III. Physiologic and psychologic aspects of food intake of obese children. *Am. J. Dis. Child.* 59:759-781, 1940.
57. *Idem*. Obesity in relation in puberty. *J. Pediatr.* 19:365-375, 1941.
58. Nathanson, I. T., and Aub, J. C. Unpublished data.
59. Werner, S. C. Adiposogenital dystrophy: a study of untreated "Fröhlich's syndrome" without brain tumor. *J. Clin. Endocrinol.* 1:134-137, 1941.
60. Schlutz, F. W. What to do about the fat child at puberty. *J. Pediatr.* 19:376-381, 1941.
61. Kunstadter, R. H. Adiposogenital dystrophy. *J. A. M. A.* 117:1947, 1941.
62. McCullagh, E. P., and Tupper, W. R. Anorexia nervosa. *Ann. Int. Med.* 14:817-838, 1940.
63. Magendanz, H., and Proger, S. Anorexia nervosa or hypopituitarism? *J. A. M. A.* 114:1973-1983, 1940.
64. Farquharson, R. F. Anorexia nervosa. *Illinois M. J.* 80:193-200, 1941.
65. Stephens, D. J. Anorexia nervosa: endocrine factors in undernutrition. *J. Clin. Endocrinol.* 1:257-268, 1941.
66. Aub, J. C., and Nathanson, I. T. The value of sex hormone assays in differential diagnosis of puberty. *Tr. A. Am. Physicians* 55:306, 1940.
67. Fraser, R., and Smith, P. H. Simmonds' disease or panhypopituitarism (anterior): clinical diagnosis by the use of two objective tests. *Quart. J. Med.* 10:297-330, 1941.
68. Rahman, L., Richardson, H. B., and Ripley, H. S. Anorexia nervosa with psychiatric observations. *Psychosom. Med.* 1:335-365, 1939.
69. Escamilla, R. F., and Lissner, H. Simmonds' disease. A clinical study with review of the literature; differentiation from anorexia nervosa by statistical analysis of 595 cases, 101 of which were proved pathologically. *J. Clin. Endocrinol.* 2:65-96, 1942.
70. Sheehan, H. L. Simmonds' disease due to post-partum necrosis of the anterior pituitary. *Quart. J. Med.* 8:277-309, 1939.
71. Doane, J. C., Blumberg, N., and Teplick, G. Simmonds' cachexia. *Endocrinology* 27:766-775, 1940.
72. Hart, J. F., and Magid, M. Blood sugar in case of complete hypophysectomy. *Arch. Int. Med.* 68:893-897, 1941.
73. Mogensen, E. Three cases of Simmonds' syndrome; with special reference to clinical diagnosis and hormone treatment. *Acta med. Scandinav.* 105:378-394, 1940.
74. Stephens, D. J. Pituitary and adrenocortical insufficiency: use of sodium chloride in the treatment of hypopituitarism. *J. Clin. Endocrinol.* 1:109-112, 1941.
75. Means, J. H. Hypothyroidism: diagnosis and treatment. *Bull. New York Acad. Med.* 16:14-19, 1940.
76. Mogensen, E. Spontaneous hypoglycemia in Simmonds' disease. *Endocrinology* 27:194-199, 1940.
77. Vaughan, W. W. The place of irradiation in acromegaly: report of fifty-three cases. *Am. J. Roentgenol.* 40:660-668, 1938.
78. Weinstein, A. The response of acromegaly to deep roentgen-ray therapy: a case report. *Ann. Int. Med.* 13:715-721, 1939.
79. Coggeshall, C., and Root, H. F. Acromegaly and diabetes mellitus. *Endocrinology* 26:1-25, 1940.
80. Courville, C., and Mason, V. R. The heart in acromegaly. *Arch. Int. Med.* 61:704-713, 1938.
81. Davis, A. C. Acromegaly: the thyroid gland in 166 cases of acromegaly. *J. Clin. Endocrinol.* 1:445-449, 1941.
82. Broster, L. R. The differential diagnosis of Cushing's syndrome (basophilism) of pituitary or adrenal origin. *Brit. M. J.* 1:425-428, 1940.
83. Dorfman, R. I., Wilson, H. M., and Peters, J. P. Differential diagnosis of basophilism and allied conditions. *Endocrinology* 27:1-15, 1940.
84. Wintersteiner, O. The adrenogenital syndrome. *J. A. M. A.* 116:2679-2683, 1941.
85. Kepler, E. J., and Keating, F. R. Diseases of the adrenal glands. II. Tumors of the adrenal cortex, diseases of the adrenal medulla and allied disturbances. *Arch. Int. Med.* 68:1010-1036, 1941.
86. Albright, F., Parson, W., and Bloomberg, E. Cushing's syndrome interpreted as hyperadrenocorticism leading to hyperglucocorticism: results of treatment with testosterone propionate. *J. Clin. Endocrinol.* 1:375-384, 1941.
87. Rakoff, A. E., Cantarow, A., and Paschkis, K. E. Cushing's syndrome. *J. Clin. Endocrinol.* 1:912-915, 1941.
88. Rock, J. Ovulation. *New Eng. J. Med.* 225:910-917, 1941.
89. Brown, W. E., Bradbury, J. T., and Metzger, I. Are the anterior pituitary-like substances gonadotropic? A clinical evaluation in woman. *Am. J. Obst. & Gynec.* 41:582-588, 1941.
90. Huber, C. P., and Davis, M. E. The clinical use of gonadotropic hormone from pregnant mare serum. *Surg., Gynec. & Obst.* 70:596-1005, 1940.
91. Lloyd, R. S., and Rubinstein, B. B. Multiple ova in the follicles of juvenile monkeys. *Endocrinology* 29:1008-1014, 1941.
92. Vogt, W. H., and Sexton, D. L. Treatment of menstrual disorders with pregnant mares' serum. *Am. J. Obst. & Gynec.* 42:81-86, 1941.
93. Brewer, J. I., Jones, H. O., and Skiles, J. H. Effect of gonadotropic substance on ovulation: results of the intramuscular use of a preparation of high potency from pregnant mare serum. *J. A. M. A.* 118:278-283, 1942.
94. Greenblatt, R. B. Histologic changes in the ovary following gonadotropin administration. *Am. J. Obst. & Gynec.* 42:983-996, 1941.
95. Gusman, J., and Goldzieher, M. A. Synergism between pituitary extracts and chorionic gonadotropins. *Endocrinology* 29:931-933, 1941.
96. Buxton, C. L. The effects of certain gonadotropic extracts on anovulatory cycles and amenorrhea. *Am. J. Obst. & Gynec.* 42:236-241, 1941.
97. Hamblen, E. C., Cuyler, W. K., Wilson, J. A., and Pullen, R. L. Endocrine therapy of functional menometrorrhagia and ovarian sterility. IV. One-two cyclic therapy with equine and chorionic gonadotropins. *J. Clin. Endocrinol.* 1:749-753, 1941.
98. Rea, C. E. Further report on the treatment of the undescended testes by hormonal therapy at the University of Minnesota Hospitals. *Surgery* 7:828-835, 1940.
99. Thompson, W. O., and Heckel, N. J. Endocrine treatment of cryptorchidism. *J. A. M. A.* 117:1953-1956, 1941.
100. Lurie, L. A., and Hertzman, J. Linear growth and epiphyseal closure. *J. Clin. Endocrinol.* 1:717-725, 1941.
101. Zelson, C., and Steinitz, E. Treatment of cryptorchidism with chorionic gonadotropic hormone and male sex hormone. *J. Pediatr.* 17:315-321, 1940.
102. Young, F. G. The pituitary gland and carbohydrate metabolism. *Endocrinology* 26:345-351, 1940.
103. Haist, R. E., Campbell, J., and Best, C. H. The prevention of diabetes. *New Eng. J. Med.* 223:607-615, 1940.
104. Spiegelman, A. R. Influence of estrogen on the insulin requirement of the diabetic. *Am. J. M. Sc.* 200:228-234, 1940.
105. Young, F. G. Influence of oestrogens on experimental canine diabetes mellitus. *Lancet* 1:600, 1941.
106. Lawrence, R. D., and Madders, K. Human diabetes treated with oestrogens. *Lancet* 1:601, 1941.
107. Goldman, S. F., Goldman, A., and Kurzrok, R. The treatment of menopausal hyperthyroidism with estrogenic substance. *New York State J. Med.* 40:1178-1184, 1940.
108. Starr, P., and Pomeroy, H. Therapeutic studies in hyperthyroidism. *Ann. Int. Med.* 15:226-243, 1941.
109. Means, J. H. The eye problems in Graves' disease. *Illinois M. J.* 80:135-138, 1941.
110. Aird, R. B. Experimental exophthalmos and associated myopathy induced by the thyrotropic hormone. *Ann. Int. Med.* 15:564-581, 1941.
111. Friedgood, H. Clinical applications of studies in experimentally induced exophthalmos of anterior pituitary origin. *J. Clin. Endocrinol.* 1:804-812, 1941.

# CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTE-MORTEM AND POST-MORTEM RECORDS AS USED  
IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

## CASE 28191

### PRESENTATION OF CASE

A fifty-four-year-old Italian housewife was admitted to the hospital because of pain in the right shoulder blade.

The patient was in good health until seven months before entry, when she began to lose weight and developed a dull aching pain in the area of the right shoulder blade. The pain was not related to meals, exertion, posture or time of day. It varied greatly in intensity, sometimes remitting completely. At times, it radiated down the right arm to the hand, and on other occasions it extended to the left shoulder blade. Throughout the illness, there were transient periods of low fever, with occasional chills and night sweats. At times, there was a slight cough. Strength and weight were progressively lost, the latter to the extent of 27 pounds during the illness. Nine months before entry, the menses (previously regular) ceased. Slight nasal bleeding occurred at the times of some of the expected periods. The appetite became poor early in the illness. Gaseous eructations, unaccompanied by nausea or vomiting, frequently followed meals. Concomitantly, the patient's previous bowel regularity was replaced by alternating bouts of constipation and diarrhea. Borborygmi and griping lower abdominal pains accompanied the constipation, whereas the alternating periods of four or five watery stools a day were painless. The patient had worked in a chocolate factory until four years before entry. She was accustomed to a glass of wine with meals. The past and family histories were irrelevant.

On admission, the patient appeared fairly well developed, but emaciated, seeming ten years past the stated age. The skin was sallow, and the mucous membranes were pale. The pupils were small and slightly irregular. The fundi showed arteriosclerotic changes. The tonsils were large and cryptic. A few pea-sized lymph nodes lay in the right anterior part of the neck. The breasts were atrophic. There were dullness and diminished tactile fremitus and breath sounds over the left upper lobe of the lung, anteromedially. The heart sounds were loud over this area. Posteriorly, over the right upper lobe, there was impaired resonance, with diminished tactile fremitus, breath sounds and voice sounds. The left border of the heart was

displaced 2 cm. beyond the midclavicular line; the pulmonic second sound was greater than the aortic, and the mitral first sound was loud. A systolic murmur was loudest over the pulmonary area, but could be heard well out in the axilla. The abdomen was flat and soft. A large, firm mass consistent with liver and moving with respirations extended 9 cm. below the costal margin. Traube's space was diminished. The spleen was not palpable. Vaginal and rectal examination showed the cervix displaced to the left, and the uterus fixed in retroversion. The pelvic contents seemed "bound down," and there was some question of a polypoid mass high in the rectum. The pulse was of Corrigan type, regular at 95, and faint pistol-shot sounds were audible over the femoral arteries.

The respirations were 20, and the temperature was 99.5°F. The blood pressure was 130 systolic, 55 diastolic.

Examination of the blood showed a red-cell count of 3,200,000 with 7.5 gm. hemoglobin, and a white-cell count of 15,800 with 84 per cent polymorphonuclears, 11 per cent lymphocytes and 5 per cent monocytes. The van den Bergh reaction was normal. The serum albumin was 3.7 gm. and the globulin 2.7 gm. per 100 cc. The nonprotein nitrogen was 20 mg. per 100 cc. A bromsulphalein test showed 15 per cent retention of the dye. The urine showed a ++ test for albumin, with 80 to 100 white cells, a few red blood cells and many bacteria per high-power field in the sediment. Urine culture yielded colon bacilli.

An electrocardiogram was within normal limits.

Roentgenograms of the chest showed a mass measuring 12 by 11 by 10 cm. in the posterior portion of the right upper lobe, displacing the trachea to the left (Fig. 1). The intercostal spaces in the region of the mass were slightly wider than those on the left side. Multiple round shadows were spread throughout the remainder of both lung fields. There was destruction of the medial end of the twelfth left rib. The liver shadow was large.

No therapy was instituted. The temperature gradually fell to 97°F., and the patient failed progressively. Death occurred on the tenth hospital day.

### DIFFERENTIAL DIAGNOSIS

DR. LOWREY F. DAVENPORT: We are given enough evidence to say that this patient definitely had a malignant tumor. The crux of our problem is to decide where the tumor originated, whether the tumor mass seen in the x-ray film was primary in the lung or metastatic from some other focus.

May we see the films?

DR. AUBREY O. HAMPTON: In addition to the area of destruction described in the record, the pa-

rule that epidermoid cancer invades the lymphatics, but not the blood stream?

DR. MALLORY: Yes; I think that is probably so.

DR. DAVENPORT: I shall make as my diagnosis a primary malignant tumor in the liver, probably developing on a cirrhotic background, with metastases to the lungs and with inflammation in the pelvis binding down the uterus and involving the lower gastrointestinal tract, which may or may not have been a part of the terminal picture. The transient bouts of fever and the occasional chills and night sweats go well with infection in the liver, but could occur with tumor and may have been partly due to breakdown of a tumor mass in the liver.

DR. MALLORY: Dr. Hampton, have you any further comment?

DR. HAMPTON: As one looks at the chest films, one can see that the spleen is not enlarged, and according to Dr. Richard Schatzki,\* primary carcinoma of the liver is commonly associated with advanced cirrhosis. The cases that he reported had large spleens, and varices in the esophagus. I wonder how we can explain the absence of enlargement of the spleen.

DR. EDWARD F. BLAND: Someone might wonder what I had to do with this case, but it so happens that I was visiting on the medical ward for Dr. J. H. Means, who was away. Dr. W. M. Jeffries, the senior house officer, and I took this case up in some detail, and we reasoned somewhat as Dr. Davenport did, but did not go quite so far in regard to the liver. The patient was too sick to have many special diagnostic procedures performed. The X-ray Department strongly implied that they thought this was a primary malignant lesion of the lung. We were inclined to metastatic involvement of the lungs because of the preceding gastrointestinal symptoms. I think our final diagnosis was metastatic carcinoma of the lungs, liver and bones from an undetermined focus, but probably in the gastrointestinal tract. Those of us who palpated the abdominal mass believed it to be liver with metastatic involvement.

DR. DAVENPORT: What did you think of the polyp in the rectum?

DR. BLAND: We could not identify it.

DR. F. DENNETTE ADAMS: Did anyone give thought to the pancreas?

DR. BLAND: We did not.

DR. ADAMS: The woman had diarrhea, loss of weight and digestive symptoms.

DR. HAMPTON: We have not seen metastases to the lung from either pancreas or liver with that appearance. I vote against the liver or pancreas.

\*Schatzki, R. Roentgenological diagnosis of primary carcinoma of the liver. *Am. J. Roentgenol.* 46:476-483, 1941.

A PHYSICIAN: I believe that the rectum was involved.

DR. DONALD S. KING: I should guess that the primary site was the lungs. We have one case—there is always one!—with metastasis to the contralateral lung. I do not quite see why metastases to the liver and bones and so forth, would not account for all the symptoms. I grant that it is an unusual x-ray picture.

DR. MALLORY: It is difficult to explain metastasis to the contralateral lung from bronchiogenic cancer, but such metastasis has occurred. I think it usually results from involvement of the hilar node and extension from there into the pulmonary artery, which permits seeding of the opposite lung. We occasionally see tuberculosis spread by that method, and it is possible with cancer but certainly unusual.

DR. FLETCHER H. COLBY: It still could be a lesion of the kidney. The unusual thing is the massive tumor mass, but I should still say that the patient could have had a renal-cell carcinoma.

DR. HAMPTON: That is a possibility, but the films do not look right. Lymphoma is the next thing we should consider, I think.

DR. MALLORY: Have you ever seen nodules as discrete as that with lymphoma in the lung?

DR. HAMPTON: Once; but not so many and perhaps not quite so smooth and sharp.

DR. DAVENPORT: Is it not true that one can have a tremendous tumor mass in the liver, and no demonstrable change in liver function?

DR. MALLORY: Yes; with metastatic, but not with primary, carcinoma.

DR. HAMPTON: What do you think of the absence of enlargement of the spleen?

DR. WILLIAM B. BREED: I think it depends entirely on the stage of advance of the cirrhosis.

DR. MALLORY: One can say that symptoms occur only in advanced cirrhosis.

DR. BREED: Then that is the answer to it. The patient should have had an enlarged spleen.

DR. MALLORY: I think Dr. Hampton has a strong point there.

DR. BREED: So do I.

#### CLINICAL DIAGNOSIS

Carcinoma of lung (? bronchiogenic), with metastases to lungs and liver.

#### DR. DAVENPORT'S DIAGNOSIS

Carcinoma of liver, with metastases to lungs.

## ANATOMICAL DIAGNOSES

Carcinoma of right kidney, with metastases to lungs, bronchial lymph nodes, vertebral bone marrow and left twelfth rib.  
Nephritis, suppurative, left, acute.  
Cystitis, diphtheritic, urinary bladder, acute.  
Emaciation, marked.  
Brown atrophy of organs.  
Leiomyomas of uterus.  
Arteriosclerosis, minimal of aorta.

## PATHOLOGICAL DISCUSSION

DR. MALLORY: Post-mortem examination showed that the primary tumor was a hypernephroma. The right kidney was nearly twice the normal size, and the liver was small—1600 gm.—and entirely normal. The lungs were studded with metastases; one extremely large one in the right upper lobe was immediately subpleural on the posterior surface of the lung and did not connect with any bronchus. One of the smaller metastases had invaded a bronchus and started to grow as a plug of tumor tissue up the bronchus, so that as a matter of fact if the patient had been bronchoscoped a biopsy would have proved the diagnosis without any question.

DR. HAMPTON: Which bronchus?

DR. MALLORY: It was the main bronchus of the left upper lobe.

DR. HAMPTON: I wondered about that. This wedge-shaped shadow in the left upper lobe bothered me, but I did not mention it. There is some atelectasis in that area.

DR. BLAND: I might say that the edge of the liver was 9 cm. below the costal margin, but the patient was emaciated.

DR. RICHARD CLARKE: At the time of post-mortem examination, was the liver down, or was it up at the costal margin?

DR. MALLORY: It was 2 cm. below the costal margin.

A PHYSICIAN: Can the kidney rotate the liver downward?

DR. MALLORY: I think it was the kidney that was felt. It was the right kidney that contained the tumor, and I can remember a kidney that I mistook for liver once.

DR. DAVENPORT: Only one thing bothers me. Why was the liver function so depressed?

DR. ALFRED KRANES: The only evidence of depression was the 15 per cent dye retention. The test is not extremely reliable.

DR. MALLORY: There was a somewhat low serum protein. On the other hand, the patient had a severe pyelonephritis on the other side. The right kidney was almost completely replaced by tumor, and the left kidney showed an active pyelonephritis. Accordingly, I think the kidneys could have been responsible for the low serum protein.

A PHYSICIAN: Was there a tumor in the rectum?

DR. MALLORY: There was a fibroid on the posterior surface of the uterus.

DR. COLBY: Was there anything else in the pelvis?

DR. MALLORY: Nothing.

## CASE 28192

## PRESENTATION OF CASE

*First admission.* A twenty-nine-year-old electric welder was admitted to the hospital because of recurrent masses in the groin.

Fifteen years before entry, the patient first noticed a swelling in the right groin. Ten years later, because of enlargement of this mass, a biopsy was taken in a community hospital and reported as "lymphoblastoma." Subsequently, the patient was given roentgen-ray treatments to each groin about once a year. Except for occasional slight pain over the right upper leg anteriorly, persistent swelling in the right groin remained the sole symptom until six weeks before entry, when occasional severe gnawing pain unrelated to meals appeared in the upper abdomen and radiated down to the pubis. During intervals between the attacks of pain, the abdomen was frequently sore. Concomitantly, the patient began to feel listless and tired, and lost about 7 pounds of weight. A few days before entry, he had several chills, accompanied by a fever of 104°F. The lump in the right groin showed no recent swelling, and the patient was not aware of any other masses.

The past and family histories were irrelevant.

On admission, the patient appeared well developed and nourished, with a warm dry skin. The throat was somewhat reddened. A few rather small lymph nodes were palpable in the front of the neck on each side, and a few similar nodes were felt in each groin. The heart and lungs were normal. The abdomen was tense and firm, without definite tenderness. The liver and spleen were not palpable. The extremities were normal.

The blood pressure was 115 systolic, 80 diastolic. The temperature was 101.5°F., the pulse 90 and the respirations 22.

Examination of the blood showed a white-cell count of 7400 with 69 per cent polymorphonuclears, 4 per cent large lymphocytes, 14 per cent small lymphocytes and 13 per cent monocytes. A second examination showed a white-cell count of 6900, including 73 per cent polymorphonuclears, 2 per cent small lymphocytes, 23 per cent monocytes, 1 per cent eosinophils and 1 per cent basophils. The hemoglobin varied from 14.5 to 12.4 gm. The blood Hinton reaction was negative. Agglutination tests with typhoid and brucellar antigens were



negative. A blood culture was negative. The urine and stools were normal.

Roentgenograms of the gastrointestinal tract showed a normal esophagus and stomach. There was some delay of barium in the second portion of the duodenum, and deformity of the third portion due to pressure of an ill-defined extrinsic mass. The mucosa appeared uninvolved. The lower border of the liver was rather low, but the spleen was not definitely enlarged. A roentgenogram of the chest showed no evidence of disease.

Roentgen irradiation was given for five days, in total dosage of 600 r to the right groin and 100 r to the anterior liver field, followed in six days by a course of 1200 r to the posterior lumbar region. Two days after this treatment was begun, the temperature rose to 104°F., and it ranged from 101 to 104°F. for the next two weeks. Diarrhea likewise appeared, with seven or eight soft movements a day. The patient was discharged on the twentieth hospital day.

*Final admission* (eighteen days later). The patient remained at home in bed. The temperature continued high, and he experienced occasional chills. He felt quite weak, and the diarrhea gradually subsided.

On re-entry, physical examination was essentially as before. Areas of first-degree roentgen dermatitis appeared over the epigastrium and lumbar spine.

Laboratory studies, including three negative blood cultures, were essentially as before, with the addition of a normal lumbar puncture, a negative stool culture, and a tuberculin reaction that was weakly positive in a dilution of 1:50,000.

A roentgenogram of the chest showed generalized miliary lesions, involving both lungs entirely, and seeming most like miliary tubercles. There was no evidence of pleural fluid, or of enlargement of hilar or mediastinal lymph nodes. A questionable area of localized infiltration 1.5 cm. in diameter lay in the right apex.

In the course of a month, the patient had remittent fever, the temperature varying from 101 to 104°F. and spiking each afternoon. The pulse was correspondingly high. Roentgen therapy was given to the lung fields in doses of 600 r to the left and 750 r to the right. Subsequent roentgenograms taken four and twelve days after this first examination showed a slight increase in the miliary lesions, and no change thereafter. In the second and third weeks in the hospital, abdominal fluid began to accumulate. Paracentesis yielded 2500 cc. of turbid green sterile fluid with a specific gravity of 1.010. The centrifugate showed only acute inflammatory cells, with no evident organisms or tumor cells. The patient continued to fail rapidly, dying on the thirty-first hospital day.

## DIFFERENTIAL DIAGNOSIS

DR. MYLES P. BAKER: On the first admission, the diagnostic problem was that of a patient with upper abdominal pain present for six weeks, associated with fatigue, chills and fever. The locus of the pain appears to have been just above the umbilicus, probably in the midline, and it was crampy pointing to something associated with the small intestine. There were several important features of the physical examination at the time of this admission. The first was the absence of generalized lymphadenopathy. I take it from the description that there was no massive swelling in either groin and that no large mass had been present for many years. Since x-ray examination of the chest was negative, we have no proof or evidence of mediastinal lymph-node enlargement, and there was no enlargement of the spleen. Moreover, there was x-ray evidence of an extrinsic mass, pressing on the third part of the duodenum, which might well have contributed to the upper abdominal crampy pain that had been one of his chief complaints. Finally, there was a distinctly unsatisfactory reaction to what was presumably adequate radiation therapy for a lymphomatous disorder. The blood picture is emphasized here. I can only say that the increase in monocytes is interesting but not necessarily associated with tubercle formation. It is obvious that those responsible for this man's care hoped that he had a radiosensitive lymphoma and treated him accordingly. They must have been dissatisfied with the effect of the treatment and discharged him with a distinctly poor prognosis and, I should think, with considerable doubt that the previous biopsy diagnosis of lymphoblastoma had been correct.

Against the diagnosis of lymphoma is the clinical course. It must be rare to have lymphoma localized in the groin for fifteen years—from the age of fourteen to twenty-nine. We do not know from the story whether the x-ray treatment approximately once a year effected any demonstrable decrease in the size of this solitary swelling. Presumably, it did, but there is no evidence to that effect. Lymphoma in a boy in his teens or early twenties is apt to progress without long remissions, and since this man had rather scanty treatment, I think the duration is distinctly against the diagnosis and brings up the question whether this could have been tuberculous adenitis from the start.

On the second admission, the patient returned with the same fever, in addition to positive x-ray findings in the chest, only three or four weeks after the previous negative chest plates. On this admission, along with the negative blood cultures and negative lumbar puncture, he had a weakly

positive tuberculin reaction to a relatively high dilution of tuberculin.

I should like to ask Dr. Hampton to comment on the chest x-ray films.

DR AUBREY O. HAMPTON: This series of films extends over a period of a year and seven months, and for the first seventeen months the chest was normal. At the time of entry into the hospital with fever, it shows this milary process in the lung; a very fine, diffuse, symmetrical process, without anything else—no enlargement of the lymph nodes, no areas of consolidation, no fluid and no areas of calcification. After the x-ray treatment, it appears that the chest is no better, and the milary lesions are larger. Examination of the spine, which was done on the outside, is not reported. In our films, the body of the fifth lumbar vertebra is uniformly dense. One can see bone trabeculae in it, and if the patient were not so young, I should have to say that he had Paget's disease. It is true, however, that lymphoma produces new bone formation in bones that appears somewhat like that, particularly if it has been treated.

The pressure defect in the duodenum is not very obvious in this film. It must have been more obvious to the man who fluoroscoped the patient, at any rate, there is some spasm and delay in the third portion of the duodenum as it crosses the spine. The liver shadow is rather faint in the lower portion and not very large. The spleen does not appear to be very enlarged. The hands and feet were examined, I suppose, to discover sarcoid; no abnormalities are present.

DR BAKER: What about the interpretation of the right apex during the second admission?

DR HAMPTON: I cannot be absolutely sure that the apexes are not similar to the rest of the lung. Certainly, there was nothing in the apex two months before.

DR BAKER: Could you rule out metastatic carcinoma on the basis of the x-ray films on the second admission?

DR HAMPTON: I think we have seen one case in this hospital with a fine milary process and to be metastatic carcinoma.

DR DONALD S. KING: Even that case is unproved.

DR BAKER: The question comes up, What lesions can produce this kind of milary process in the lungs? First of all, the likeliest is tuberculosis. With such a diagnosis, I think the weakly positive skin tuberculin test is consistent in a sick person.

DR ALLEN G. BRALEY: The dilution was 1:50,000.

DR BAKER: I beg your pardon. Then we shall have to say that the strongly positive tuberculin

test is going to be somewhat difficult to explain in such a sick person.

Lymphoma has been reported as giving an x-ray picture that is difficult to distinguish from milary tuberculosis. If lymphoma affects the lung parenchyma, it is much more likely to do so in the form of peribronchial infiltration or as an isolated nodule. It may be the site of cavity formation or it may take the form of pneumonia with or without atelectasis, but this would be a distinctly rare x-ray picture with lymphoma.

The other possibilities can be ruled out on the clinical story alone, such as silicosis, which usually gives coarser mottling than this. Yeast infections run a more benign course, and do not give the picture of such an acutely sick patient. One or two patients that I have seen with sarcoid, in whom the x-ray picture was consistent with milary tuberculosis, have been in much better health than this man was. I have followed one daily over a course of five years, and at no time was she at all ill, she was always ambulatory, had no symptoms except those referred to her iritis, and now, five years after the onset of the iritis, her chest is almost entirely clear. This is not true of the case under discussion. We are dealing with a man who was in his last month of life at the time when he developed this picture of milary seeding. I think we can rule out a relatively benign process such as sarcoid on that basis. We have, as Dr. Hampton said, little reason to suspect metastasis to the lungs from a retroperitoneal mass such as sarcoma.

Could this man have developed milary tuberculosis with a positive x-ray plate only six weeks after his film had been negative? That is possible, and although I cannot cite a definite case to back me up, I think that the likeliest diagnosis here is not lymphoma but tuberculous adenitis, with retroperitoneal tuberculous lymph nodes and acute hematogenous spread of infection, with a picture of milary tuberculosis at the end, and tuberculous peritonitis. The accumulation of ascitic fluid with a low specific gravity is not diagnostic and could occur in lymphoma as well as in tuberculosis; I should be inclined, however, to dismiss the tuberculin test on the basis of the clinical story and x-ray findings and make a diagnosis of generalized tuberculosis as the most likely explanation for this man's signs.

A PRINCIPAL: What is the effect of radiation on tuberculous adenitis?

DR HAMPTON: It was used for many years in the treatment with a dosage such as this patient had. I suppose the majority of people who treated such patients believed they improved. Much larger doses were given to active tuberculosis in the lung,

with the hope of fibrosing the process, and some workers have said that it improved active tuberculosis of the lung. I have done this accidentally, without any known effect. We had no hesitancy in treating this patient, even though our own first diagnosis was miliary tuberculosis, because if he had it, he had no hope of living, and if he had lymphoma we might put off death for a while. We gave a dose that we thought was safe even if he had miliary tuberculosis and could survive.

A PHYSICIAN: Does lymphoma never give a picture like this?

DR. HAMPTON: In the X-ray Department, we had quite a discussion about this case. In all the follow-ups on lymphoma, we have not seen a single example of a miliary process similar to this. We have had cases showing numerous nodules from 1 to 5 cm. in diameter but not a miliary process. We all admitted that some day we shall probably see one; there is no reason to suppose that we shall not.

A PHYSICIAN: Would this picture be consistent with septic infarcts?

DR. HAMPTON: I do not believe so.

#### CLINICAL DIAGNOSES

Diffuse lymphoma.

Miliary tuberculosis?

#### DR. BAKER'S DIAGNOSIS

Miliary tuberculosis, generalized.

#### ANATOMICAL DIAGNOSES

Miliary tuberculosis, generalized.

Tuberculous ulceration of duodenum, with perforation.

Tuberculosis of retroperitoneal lymph nodes.

Tuberculous enteritis, moderate.

Thrombosis of left adrenal vein.

Interadherence of aortic cusps, probably congenital.

Pulmonary edema, moderate, bilateral.

Tuberculous meningitis.

#### PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: Post-mortem examination showed very voluminous lungs, densely seeded, from top to bottom on both sides, with miliary

tubercles; some nodules were considerably larger than miliary tubercles, reaching 1 cm. in diameter. There was a slight tuberculous peritonitis. The duodenum was unusual. A large ulcer was found beyond the papilla in the third portion, where the duodenum crosses the vertebral column. We had never seen a peptic ulcer beyond the papilla of Vater, and later examination showed that the walls of this ulcer were caseous and it was purely tuberculous in origin. It communicated with a retroperitoneal abscess cavity, and whether the tuberculosis was primary in the duodenum, spreading through the intestinal wall, or a tuberculous retroperitoneal lymph node spread in the reverse direction into the duodenum, we cannot say. There were multiple tuberculous ulcers in the colon, several isolated tubercles in the meninges over the cerebellum and very early diffuse terminal tuberculous meningitis. There were peculiar lesions in the kidney and heart that did not look like tubercles but like septic abscesses, each about 1 cm. in diameter and filled with green purulent material, which grossly did not remotely suggest caseation, but later examination proved that these were also pure tuberculous abscesses. I have never seen a case of tuberculosis in which tubercle bacilli were so numerous. They even showed up in great numbers in the sections stained with eosin and methylene blue.

DR. HAMPTON: I think we can trace the origin of this process on the x-ray films. The gastrointestinal examination was done two months before death. At that time, the patient had this indefinite outline of the third portion of the duodenum, with an extrinsic mass and normal lung. One can assume that tuberculous adenitis was primary because the mucosa of the duodenum is not grossly abnormal and no definite ulcer is seen.

A PHYSICIAN: Was the mass in the groin tuberculous?

DR. MALLORY: A small caseous nodule 1 cm. in diameter was found there. There was no evidence of lymphoma.

DR. BAKER: Were there any sputum examinations for tubercle bacilli on the second admission?

DR. MALLORY: No.

A PHYSICIAN: Would you doubt now the diagnosis of lymphoblastoma on the previous biopsy?

DR. MALLORY: Completely.

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established in 1828

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND  
PUBLISHED UNDER THE JURISDICTION OF THE  
COMMITTEE ON PUBLICATIONS

Official Organ of  
THE MASSACHUSETTS MEDICAL SOCIETY  
and  
THE NEW HAMPSHIRE MEDICAL SOCIETY

## EDITORIAL BOARD

Joseph Garland M.D.	Stephen Rushmore M.D.
William B. Breed M.D.	Henry R. Viets M.D.
George R. Minor M.D.	Robert M. Green M.D.
Frank H. Lahey M.D.	Charles C. Lund M.D.
Sheldon Warren M.D.	John F. Fulton M.D.
George L. Tobey, Jr. M.D.	A. Warren Stearns M.D.
C. Guy Lane M.D.	Dwight O. Hara M.D.
William A. Rogers M.D.	Chester S. Kefauver M.D.

## ASSOCIATE EDITORS

Thomas H. Larnham, M.D.	Donald Munro M.D.
Henry Jackson, Jr., M.D.	

Walter P. Bowers M.D., EDITOR EMERITUS  
Robert N. Nye M.D., MANAGING EDITOR  
Clara D. Davies ASSISTANT EDITOR

**SUBSCRIPTION TERMS** \$6.00 per year in advance postage paid for the  
United States (medical students \$3.50 per year), Canada, \$7.04 per year  
Foreign \$9.52 per year for all foreign countries belonging to the  
Postal Union

**MATERIAL** for early publication should be received not later than noon  
on Friday

The Journal does not hold itself responsible for statements made by any  
contributor

Communications should be addressed to the *New England Journal of  
Medicine* 8 Fenway Boston Massachusetts

## PROCUREMENT AND ASSIGNMENT SERVICE

The mailing of the enrollment forms and  
questionnaires for the Procurement and  
Assignment Service was completed on April  
24, and by now, every registered physician  
in the United States should have received  
them. These forms should be carefully  
filled out and **IMMEDIATELY** returned. If  
any physician has failed to receive the forms,  
he should write for them directly to the  
National Roster of Scientific and Specialized  
Personnel, 916 G Street, N. W., Washington,  
D. C.

## ANNUAL MEETING

THE one hundred and sixty-first anniversary  
of the Massachusetts Medical Society will be held  
at the Hotel Statler. The program of the meeting,  
which will be held on Monday, Tuesday and  
Wednesday, May 25, 26 and 27, appears elsewhere  
in this issue of the *Journal*.

The outstanding change in the usual sequence  
of events is one designed to permit all fellows of  
the Society to enjoy the scientific meetings more  
thoroughly than they have in the past; hence, the  
annual meetings of the supervising censors and  
Council will be held in the late afternoon and  
evening, respectively, of Monday, May 25, the day  
before the opening of the scientific sessions and  
the annual meeting of the Society.

The scientific papers to be presented at the  
four general sessions are largely concerned with  
War Medicine, that is, the application of  
medical science to war and its associated  
activities. Addresses by Dr. Frank H. Lahey,  
president of the American Medical Association,  
Dr. Morris Fishbein, editor of the *Journal of the  
American Medical Association*, Drs. Raymond A.  
Vonderlehr and Rolla E. Dyer, of the United  
States Public Health Service, and Mr. John M.  
Pratt, executive administrator of the National  
Physicians' Committee for Extension of Medical  
Services should be of particular interest. The  
Annual Oration will follow the annual meeting  
of the Society, to be held at eleven in the morning  
on Tuesday, May 26; the orator is Dr. William B.  
Castle, and his subject "Some Remarks on Therapy  
for Anemia." Following the annual dinner that  
evening, at which the guest speakers are Drs.  
Lahey and Fishbein, the Shattuck Lecture, "Medi-  
cine and Air Supremacy," will be given by Dr. John  
F. Fulton, of New Haven, Connecticut. The  
combined luncheons and meetings of the sections  
will be held on Wednesday noon, May 27, and  
extremely interesting topics have been chosen for  
discussion. As in previous years, there will be a  
continuous motion picture program during the  
two days of general sessions. The scientific and

technical exhibits will be extensive and comprehensive and promise, more than ever, to be of great educational value.

Transportation difficulties have necessitated a curtailment of the ladies' program. No out-of-town trip could be scheduled, but there will be a reception and tea at the Hotel Statler on Tuesday afternoon, May 26, followed by a dinner at The Copley-Plaza, and a luncheon at the Women's City Club, on Wednesday, May 27.

Since the Nation *is* at war, the program is not only timely but of extreme interest and value, and for being able to plan such a meeting, in spite of the difficulties engendered by war activities, the Committee of Arrangements deserves the sincere thanks of all members of the Massachusetts Medical Society, which can best be shown by a record-breaking attendance.

---

## THE ELLA SACHS PLOTZ FOUNDATION

ACCORDING to its eighteenth annual report, the Ella Sachs Plotz Foundation for the Advancement of Scientific Investigation awarded, during the past year, thirty-five grants for research in medicine and surgery and in related branches of science. Since its establishment, the foundation has supported four hundred and twenty-nine projects in the United States and thirty-seven other countries. The maximum sum given to any single experiment or study has usually been less than five hundred dollars.

Although the original intention of the foundation, as expressed by the trustees, was to assist research on single problems in stipulated fields, the policy in recent years has been to encourage investigations in the sciences closely related to medicine, without reference to special fields. Thus, the fund now supports experiments varying in scope and purpose from research on typhus and different serologic types of hemolytic streptococci to work in endocrinology and chemical embryology and studies on the physiologic effects of high altitudes.

Of particular interest to physicians in Massachusetts are the awards that were made to Dr. George Barkan, of Boston University School of Medicine; Dr. Austin M. Brues, of the Huntington Memorial Hospital; Dr. R. W. Hickman, of the Cruft Laboratory, Harvard University; Dr. Otto Krayner, of the Harvard Medical School; Dr. Fritz Lipman, of the Massachusetts General Hospital; and the Thorndike Memorial Laboratory, Boston City Hospital. The last-named gift was in recognition of Dr. Francis W. Peabody's services to the foundation.

The dramatic events of a world engaged in total war naturally occupy our minds and obscure, but do not obliterate, the accomplishments made possible by such organizations as the Ella Sachs Plotz Foundation. We can win this struggle to preserve our national integrity and way of life only by striking with all our force against an enemy in whose philosophy there is no room for liberty, justice, decency and honor. With the victories, we must accept temporary retreats; we must learn to bear the thought of the inevitable slaughter and destruction. But the peace must also be won—and kept. The silent and untiring workers engaged in research fight an unending war in which they can never admit defeat—a struggle against the growths, the viruses, the deficiency diseases that plague mankind. It is these men who will show us how to keep and enjoy the benefits of the peace we are striving and praying for.

---

## MEDICAL EPONYM

### OSGOOD-SCHLATTER'S DISEASE

Dr. Robert B. Osgood (b. 1873), of Boston, described "Lesions of the Tibial Tubercle Occurring During Adolescence" in the *Boston Medical and Surgical Journal* (148:114-117, 1903). The author made the following statements:

The adolescent tibial tubercle, from its situation and mode of development, is susceptible to injuries, especially in athletic subjects. These lesions are usually caused by a violent contraction of the quadriceps extensor.

Fracture and complete avulsions of the tubercle are rare, cause loss of function, and are easily diagnosed, usually clinically and always by means of the x-ray.

Avulsions of a small portion and partial separation of the tubercle are more common. They do not cause complete loss of function, but without treatment, long continued serious annoyance. The diagnosis should be made by a combination of the clinical and x-ray pictures, and before the latter are accepted as evidence both knees should be skiagraphed and accurate technique observed.

Professor Carl Schlatter (1864), of Zurich, independently discussed "Verletzungen des schnabel-förmigen Fortsatzes der oberen Tibiaepiphyse [Injuries to the Beak-shaped Process of the Upper Epiphysis of the Tibia]" in Bruns's *Beiträge zur klinischen Chirurgie* (38:874-887, 1903). A portion of the translation follows:

There occurs, in the region of the knee, a typical form of injury, not very uncommon, whose clinical picture, in spite of all the recent advances in diagnosis, is not yet satisfactorily clear to us, as I realize from a fruitless search for a comprehensive study of this injury in the literature, and also from my own errors in diagnosis. This is the separation of the beak-shaped process of the upper tibial epiphysis, which encompasses the head of the tibia anteriorly.

R. W. B.

## MASSACHUSETTS MEDICAL SOCIETY

### ANNUAL MEETING OF THE COUNCIL

The annual meeting of the Council will be held in the Georgian Room of the Hotel Statler, Boston, on Monday, May 25, 1942, at 7:00 p.m. This meeting will be preceded by the Cotting supper which will be served in Parlors A, B and C of the same hotel at 6:00 p.m.

#### Business:

1. Presentation of record of the special meeting of the Council held April 15, 1942, as published in the *New England Journal of Medicine*, issue of May 14, 1942.
2. Nominating Committee retires to deliberate.
3. Reports of standing and special committees.
4. Election of officers and orator.
5. Appointment of committees for ensuing year.
6. Such other business as may lawfully come before the meeting.

MICHAEL A. TIGHE, M.D., *Secretary*

### COMMITTEE ON MATERNAL WELFARE

#### CASE HISTORY: RUPTURE IN TUBAL PREGNANCY, FOLLOWED BY DEATH

A thirty-eight-year-old housewife was seen at 10:00 a.m. by her physician. She had fainted three

times and was reported to have abdominal colic with diarrhea. At 3:00 p.m. she was sent into the hospital in shock, practically pulseless, with no blood pressure, and died a few moments after admission. The past history was irrelevant. There had been one pregnancy twelve years previously, and the child was living and well. There was no history of skipped periods, although the hospital record was most inadequate. Autopsy revealed perforation of the right tube, and the abdomen was filled with blood clots.

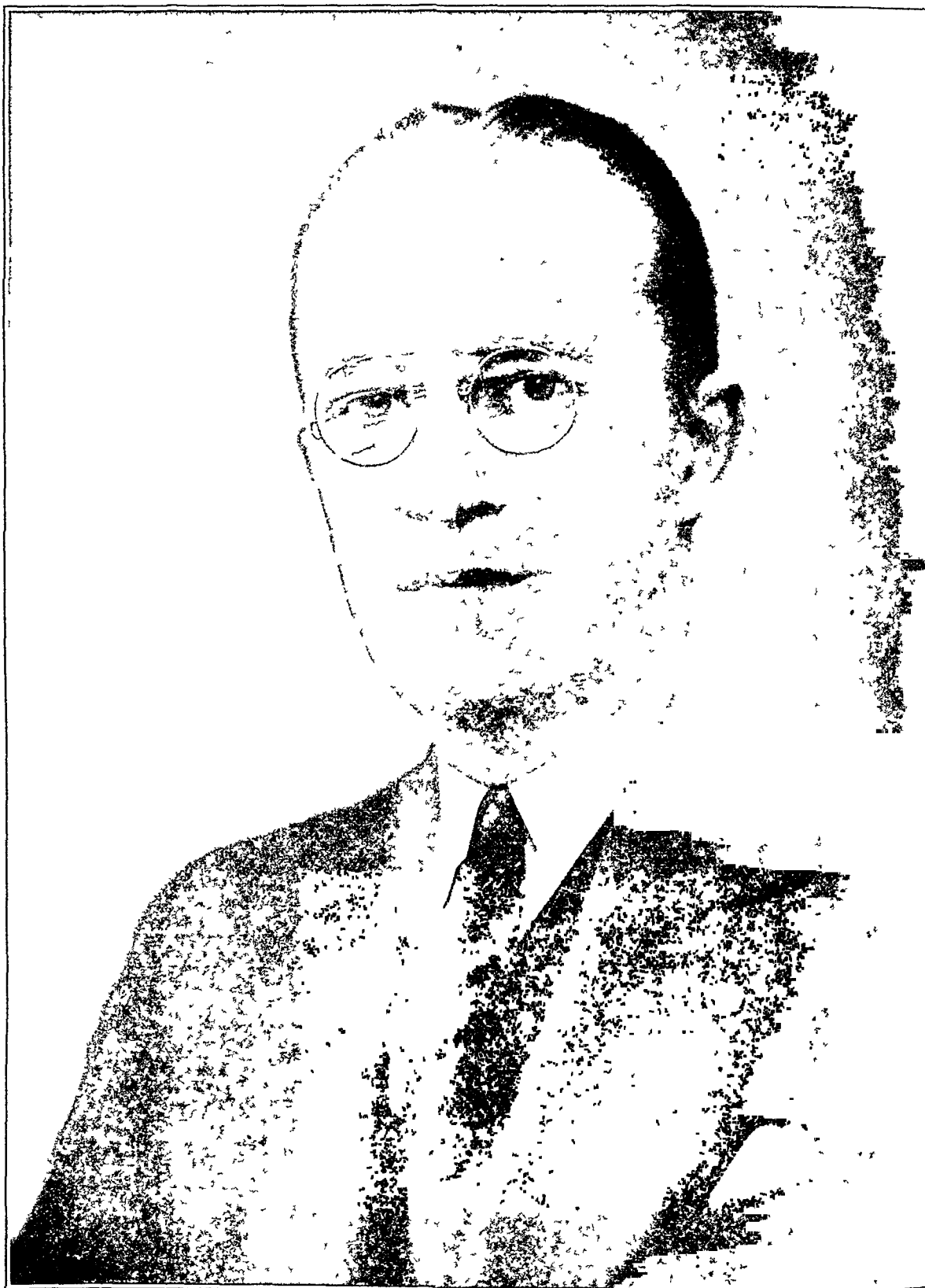
*Comment.* The inadequacy of the history is characteristic of many small hospitals in Massachusetts. The new law placing the licenses under the Massachusetts Department of Public Health will undoubtedly rectify this neglect. In all probability, if a history had been obtained and recorded, it would have stated some irregularity in the menstrual cycle immediately preceding this fatality. That five hours elapsed between the time when the patient was seen at home and her arrival at the hospital allows no interpretation except ignorance on the part of the physician who saw this patient, or utter lack of appreciation of the seriousness of her condition. Without doubt, because this patient fainted three times before she was seen by a physician, evidence of hemorrhage must have been present, had the practitioner been intelligent enough to observe it. There is, of course, no excuse for this lapse of five hours.

No specific diagnosis was made prior to death. The autopsy was performed by a medical examiner. The death certificate assigned the cause of death to internal hemorrhage, and the autopsy proved the death to have been puerperal in origin.

Whether this patient had been seen by a physician before the morning of her death is not disclosed in the record. If irregular bleeding, which certainly must have occurred, stimulated the patient to consult a physician and if medical advice was obtained, this fatality can surely be attributed solely to poor medicine. It illustrates the fact that ruptures in tubal pregnancies can bleed to the point of exsanguination, and that the only way to prevent a fatal outcome is to make the patient with irregular flowing in the early months of pregnancy understand that medical advice must be sought, and to make the physician realize that irregular flowing in the early months of pregnancy may mean a tubal pregnancy, the only intelligent treatment of which is hospitalization, vaginal examination and laparotomy, whenever there is a question of a pathologic pelvis.

## MASSACHUSETTS MEDICAL SOCIETY

OFFICERS OF THE MASSACHUSETTS MEDICAL SOCIETY, 1941-1942

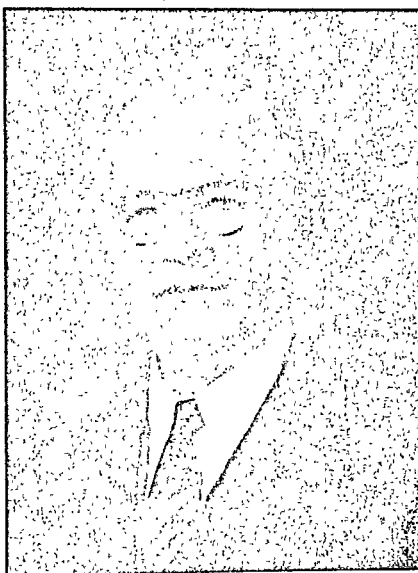


Bacl

DR. GEORGE LEONARD SCHADT, *President-Elect*



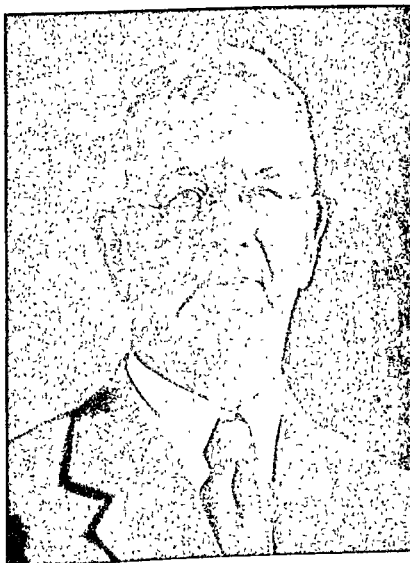
DR. FRANK R. OBER, *President*



DR. EDWARD P. BAGG, *Vice-President*



DR. MICHAEL A. TIGHE, *Secretary*



DR. CHARLES S. BUTLER, *Treasurer*



## PROGRAM OF THE ONE HUNDRED AND SIXTY-FIRST ANNIVERSARY OF THE MASSACHUSETTS MEDICAL SOCIETY

Monday, Tuesday and Wednesday, May 25, 26 and 27, Hotel Statler, Boston

The exercises of the one hundred and sixty-first annual meeting of the Society will be held at the Hotel Statler, Boston, on Monday, Tuesday and Wednesday, May 25, 26 and 27. It should be noted that the program for the first day, Monday, May 25, provides no scientific session; the golf tournament at the Commonwealth Country Club is scheduled for the afternoon, and the annual meetings of the supervising censors and Council for the late afternoon and evening, respectively.

The Committee of Arrangements, which has planned the meeting, consists of Drs. William T. O'Halloran, chairman, James A. Halsted, George P. Sturgis, Henry H. Faxon and Gordon M. Morrison.

With the exception of some of the section meetings and luncheons, all activities will be located at the Hotel Statler. The scientific exhibits will fill the Ballroom Assembly, and the technical exhibits will occupy the Ballroom. On Tuesday and Wednesday, both in the morning and in the afternoon, motion pictures will be shown in the Lower Foyer.

The members' registration desk will be in the Ballroom, and that of the ladies on the Mezzanine Floor. All who attend are earnestly requested to register.

According to the arrangement a year ago, the annual dinner will be followed by the Shattuck Lecture, the dinner being scheduled to start at 7:00 p.m., Tuesday.

The luncheon meetings of the sections will be held Wednesday noon. Since it is necessary to have some idea of the number of members at these luncheons, all are urged to notify the committee at once if they plan to attend.

### MONDAY EVENING, MAY 25

#### Annual Meeting of the Council of the Massachusetts Medical Society

- 5:00 **Supervising Censors' Meeting** (Hancock Room).
- 6:00 **Cotting Buffet Supper** (Parlors A, B and C).
- 7:00 **Council — Annual Meeting** (Georgian Room).
- Nominating Committee** (Hancock Room).

### TUESDAY MORNING, MAY 26

#### First General Session

Georgian Room

Dr. Cadis Phipps, *Chairman*

Dr. Edward J. O'Brien, Jr., *Co-Chairman*

- 9:20 **Scarlet Fever Today.** Dr. Edwin H. Place: physician-in-chief, South Department, Boston City Hospital; clinical professor of pediatrics, Tufts College Medical School.

- 9:40 ***The Problem of Certain Tropical Diseases in War.*** Dr. Henry E. Meleney (New York City): Hermann M. Biggs Professor of Preventive Medicine, New York University College of Medicine.

- 10:00 ***Trauma of the Skin Due to Wartime Activities.*** Dr. John G. Downing: assistant professor of dermatology, Tufts College Medical School; dermatologist, Boston City Hospital and St. Elizabeth's Hospital.

- 10:20 ***Massachusetts Public-Health Problems in Wartime.*** Dr. Paul J. Jakmauh: Commissioner, Massachusetts Department of Public Health.

- 10:40 ***The Impact of the War on the Venereal Disease Problem.*** Dr. Raymond A. Vonderlehr (Washington, D. C.): Assistant Surgeon General, Division of Venereal Diseases, United States Public Health Service.

#### 11:00 **Annual Meeting of the Massachusetts Medical Society.**

Georgian Room

**Annual Oration** (following business meeting): *Some Remarks on Therapy for Anemia.* Dr. William B. Castle: professor of medicine, Harvard Medical School; associate director, Thorndike Memorial Laboratory; director, Second and Fourth Medical Services, Boston City Hospital.

**Annual Luncheon** (Parlors A, B and C): tickets may be procured at the Registration Desk.

### TUESDAY AFTERNOON, MAY 26

#### Second General Session

Georgian Room

Dr. George Leonard Schadt, *Chairman*  
Dr. Ralph R. Stratton, *Co-Chairman*

- 2:00 ***Hospital Preparedness.*** Dr. Charles F. Wilkins: executive director, Beth Israel Hospital; chief of Emergency Medical Services for Suffolk County.

- 2:20 ***Medical-School Plans for the Emergency.*** Dr. Bennett F. Avery: dean, Boston University School of Medicine; Waterhouse Professor of Anatomy, Boston University School of Medicine.

- 2:40 ***The Doctor's Role in First Aid.*** Dr. A. William Reggio: visiting surgeon, Massachusetts General Hospital; deputy director, Medical Division, Massachusetts Committee on Public Safety.

- 3-00 *Civilian Medical Defense in Massachusetts* Dr Elliott C Cutler Moseley Professor of Surgery, Harvard Medical School, surgeon-in-chief, Peter Bent Brigham Hospital, director, Medical Division, Massachusetts Committee on Public Safety
- 3-10 *American Medicine and the War* Dr Morris Fishbein (Chicago) editor, *Journal of the American Medical Association*
- 3-20 *Tuberculosis Increasing?* Dr John A Foley professor of medicine, Boston University School of Medicine, chief-of-staff, Boston Sanatorium director, Fifth and Sixth Medical Services, Boston City Hospital
- 4-00 *The Interrelationship of Anesthesia with Analgesia* Dr Joseph F McCarthy (New York City) director, Department of Urology, New York Polyclinic Medical School and Hospital
- 4-20 *Hypertension Present status of the problem* Dr Robert W Wilkins assistant professor of medicine, Boston University School of Medicine
- 4-40 *The Present Program for the Immunization of Troops* Dr John F Enders assistant professor of bacteriology, Harvard Medical School

## TUESDAY EVENING, MAY 26

### Annual Dinner of the Massachusetts Medical Society

SALLE MODERNE

7 00 pm

#### Guest Speakers:

Dr Frank H Lahey president, American Medical Association

Dr Morris Fishbein (Chicago) editor, *Journal of the American Medical Association*

*The Shattuck Lecture (GEORGIAN ROOM) (following annual dinner) Medicine and Air Supremacy* Dr John F Fulton (New Haven, Connecticut) Sterling Professor of Physiology, Yale University School of Medicine

## WEDNESDAY MORNING, MAY 27

### Third General Session

GEORGIAN ROOM

Dr A A Hornor, *Chairman*

Dr Edward P Bagg, *Co Chairman*

- 9-00 *Carcinoma of the Bronchus* Dr George W Holmes professor of clinical roentgenology emeritus, Harvard Medical School consulting roentgenologist, Massachusetts General Hospital
- 9-20 *Clinical Application of Gastrosocopy* Dr Charles W McClure junior visiting physician and gas-troscopist, Fifth Medical Service, Boston City Hospital, and Dr I R Jankelson assistant professor of medicine, Tufts College Medical School junior visiting physician, Boston City Hospital

- 9-40 *The Procurement and Assignment of Physicians during the Present Emergency* Dr Reginald Fitz Massachusetts State Chairman, Procurement and Assignment Service, Office of Defense, Health and Welfare Services
- 10-00 *The Relation of Medicine to the Emergency* Dr Frank H Lahey president, American Medical Association, chairman, Procurement and Assignment Service director of surgery, Lahey Clinic, surgeon-in-chief, New England Deaconess Hospital and New England Baptist Hospital
- 10-20 *Management of the Acute Stage of Infantile Paralysis* Dr Frank R Ober John B and Buckminster Brown Clinical Professor of Orthopaedic Surgery, Harvard Medical School, chief of Orthopedic Department, Children's Hospital, orthopedic surgeon, Peter Bent Brigham Hospital, chief surgeon, New England Peabody Home for Crippled Children
- 10-40 *Typhus Fever* Dr R E Dyer (Bethesda, Maryland) director National Institute of Health, United States Public Health Service
- 11-00 *Industrial Health in National Defense* Dr Daniel L Lynch medical director, New England Telephone and Telegraph Company
- 11-20 *A Further Report on Para Aminobenzoic Acid and Its Relation to Gray Hair* Dr Benjamin F Sieve instructor in medicine, Tufts College Medical School junior visiting physician, Boston City Hospital
- 11-40 *World Conflict and Medical Service* Mr John M Pruitt (Chicago) executive administrator, National Physicians' Committee for the Extension of Medical Services

## WEDNESDAY NOON, MAY 27

### Section Meetings and Luncheons

12 00 m-2 00 pm

### Sections of Medicine and Surgery

PARLORS A, B AND C

- Dr Erwin C Miller, Worcester, *Chairman—Medicine*  
 Dr Charles L Short, Boston, *Secretary—Medicine*  
 Dr Grantley W Taylor, Boston, *Chairman—Surgery*  
 Dr James C McCann, Worcester, *Secretary—Surgery*
- The Vascular Dynamics Recognition and Management of Shock* Dr Virgil H Moon (Philadelphia) professor of clinical pathology, Jefferson Medical College of Philadelphia

### Section of Pediatrics

THE JUNIOR LEAGUE, ZERO MARLBOROUGH STREET

Dr Philip H Sylvester, Boston *Chairman*  
 Dr James Marvin Baty, Brookline, *Secretary*

*The Common Cold* Dr Francis L Weille associate surgeon, Massachusetts Eye and Ear Infirmary, assistant in otolaryngology, Harvard Medical School

**Section of Obstetrics and Gynecology**

THE TAVERN CLUB, 4 BOYLSTON PLACE

Dr. M. Fletcher Eades, Boston, *Chairman*Dr. Raymond S. Titus, Boston, *Secretary*

*Vaginal Discharge.* Dr. John Rock: visiting surgeon, Free Hospital for Women; instructor in gynecology and research associate in obstetrics, Harvard Medical School.

**Section of Radiology and Physiotherapy**

PARLORS D AND E

Dr. Joseph H. Marks, Boston, *Chairman*Dr. Henry A. Tadgell, Wrentham, *Secretary***Symposium on Bronchial Obstructions.**

Dr. Edward B. Benedict: assistant in surgery, Harvard Medical School; associate visiting surgeon, Massachusetts General Hospital.

Dr. Richard H. Overholt: thoracic surgical consultant, New England Deaconess Hospital and Corey Hill Hospital; surgeon-in-chief, Thoracic Clinic, Boston Dispensary.

Dr. Merrill C. Sosman: clinical professor of roentgenology, Harvard Medical School; roentgenologist-in-chief, Peter Bent Brigham Hospital.

**Section of Dermatology and Syphilology**

PARLOR F AND THE HANCOCK ROOM

Dr. Arthur M. Greenwood, Boston, *Chairman*Dr. William J. Macdonald, Boston, *Secretary*

*Eczema and Pruritus in the Aged.* Dr. Leonard E. Anderson: dermatologist, Out-Patient Department, Springfield Hospital; dermatologist, Wesson Memorial Hospital, Springfield.

WEDNESDAY AFTERNOON, MAY 27

**Fourth General Session**

GEORGIAN ROOM

Dr. Donald Munro, *Chairman*Dr. Frederick J. Lynch, *Co-Chairman*

2:00 *The Early Treatment of Burns.* Dr. Donald W. MacCollum: associate in surgery, Harvard Medical School; associate in plastic surgery, Peter Bent Brigham Hospital; associate visiting surgeon, Children's Hospital.

2:20 *The Five-Year Report on Cesarean Section in Massachusetts (1937-1941).* Dr. Robert L. DeNormandie: member, State and Federal Advisory Committees on Maternal and Child Hygiene.

2:40 *The Choice of Drug in the Treatment of Infections.* Dr. Charles H. Rammelkamp: instructor in medicine, Boston University School of Medicine.

3:00 *Deficiency Diseases of the Oral Cavity.* Dr. David Weisberger: instructor in oral medicine, Harvard Dental School.

3:20 *The Sequela of War Head Injuries.* Dr. Derek Denny-Brown: professor of neurology, Harvard Medical School.

3:40 *War Dermatology.* Dr. C. Guy Lane: clinical professor of dermatology, Harvard Medical School; chief of Department of Dermatology, Massachusetts General Hospital.

4:00 *Symposium on Minor Psychiatric Disturbances in War and Civilian Life.*

*The Diagnosis of Psychoneurotic Disturbances.* Dr. Donald J. MacPherson: associate in medicine, Peter Bent Brigham Hospital.

*The Psychiatric Approach in Medicine: Psychosomatic medicine.* Dr. Jacob E. Finesinger: assistant professor of psychiatry, Harvard Medical School; psychiatrist, Massachusetts General Hospital.

*Therapy in the Psychoneuroses.* Dr. Erich Lindemann: associate in psychiatry, Harvard Medical School; associate psychiatrist, Massachusetts General Hospital.

**Motion Picture Program**

LOWER FOYER

Tuesday, May 26

- 9:30-10:30 *Prevention and Treatment of Eclampsia.*  
 10:30-10:45 *Diagnostic Procedures in Tuberculosis.*  
 10:45-11:00 *Emergency Treatment for Fractures.*  
 11:00-11:30 *Technique of Blood Transfusions.*  
 11:30-12:00 *Treatment of Asphyxia Neonatorum.*  
 2:00- 2:45 *Diagnosis and Treatment of Infections of the Hand.*  
 2:45- 3:15 *First Aid in Transporting Fractures of the Leg, Spine and Arm.*  
 3:15- 3:30 *Protruded Intervertebral Disk: Diagnosis and surgical treatment.*  
 3:30- 4:00 *Cardiac Irregularities.*  
 4:00- 4:15 *Splenectomy.*  
 4:15- 4:30 *The Use of Extra Fine Catgut.*

Wednesday, May 27

- 9:30-10:30 *Sex Hormones, Physiology, Diagnosis and Therapy.*  
 10:30-11:00 *Vaginal Hysterectomy: Suture method.*  
 11:00-11:15 *Vaginal Hysterectomy: Clamp method.*  
 11:15-11:45 *Treatment of Burns.*  
 2:00- 2:15 *Transverse Cervical Cesarean Section.*  
 2:15- 2:30 *Hernioplasty.*  
 2:30- 3:15 *Physiology and Conduct of Normal Labor.*  
 3:15- 3:45 *Acute Appendicitis.*  
 3:45- 4:30 *Arteriosclerotic Heart Disease.*

**Scientific Exhibits**

BALLROOM ASSEMBLY

Booth

- S-10 *The Pathology of Skin Tumors.* Massachusetts State Tumor Diagnostic Service. Exhibitors: Dr. Shields Warren and Dr. Olive Gates.

15-16 *First Aid in Fractures* Massachusetts Committee on Fractures and Trauma, American College of Surgeons, Medical Division, Massachusetts Committee on Public Safety, Boston Metropolitan Chapter, American Red Cross

17 *Study and Treatment of Alcoholism* The Washingtonian Hospital Exhibitor Dr Merrill Moore, director of research

18 *The Senescent Skin and Its Diseases* Dr C Guy Lane, Dr Arthur M Greenwood and Dr Ethel M Rockwood

19 *Blood for Victory* Blood Donor Center, Boston Metropolitan Chapter, American Red Cross Exhibitor Mr Wesley Fuller, director

20 *Sigmoidoscopy* The Gastrointestinal Clinic, Boston City Hospital Exhibitors Dr Charles W McClure and Dr I R Jankelson

21 *Intercapillary Glomerulosclerosis* Fifth and Sixth Medical Services, Boston City Hospital Boston University School of Medicine Mallory Institute of Pathology, Boston City Hospital Exhibitors Dr Harold Jeghers and Dr Oscar Wollenman

22-24 *Biliary Tract Disease* Evans Memorial Hospital Massachusetts Memorial Hospitals, Boston

1 *Gallstones Composition and etiology* Dr Knowles B Lawrence

2 *Röntgenologic Study of the Gallbladder* Dr George Levene

3 *Pathology of Acute Cholecystitis* Dr Charles F Branch

4 *Surgical Treatment of Acute Cholecystitis* Dr Howard M Clute

5 *Duodenal Drainage* Dr Franz J Ingelinger

6 *Structures of the Common Duct* Dr Howard M Clute

7 *Gallstone Ileus* Dr Egon G Wissing and Dr Knowles B Lawrence

8 *Preoperative and Postoperative Care in Obstructive Jaundice* Dr Thomas J Anglem

25-26 *Anesthesia* Massachusetts members of the New England Society of Anesthesiology

27 *Fractures* The Faulkner Hospital Exhibitors Dr Gordon MacK Morrison and Dr Harvey R. Morrison

28-29 *New Standards of Efficiency of Treatment in Diabetes Mellitus* Dr Elliott P Joslin and associates

30-31 *Skeletal Traction and Countertraction Methods Applicable to Ordinary Extension Splints Used in the Treatment of the Fractures of the Lower Extremity Rupture of Biceps Brachii* United States Marine Hospital, Boston Exhibitor Dr Richey L Waugh

32-33 *Surgical Pathology* The Fallon Clinic Worcester Exhibitors Dr John Fallon, Dr James T Brosnan and Dr William G Moran

34 *Occupational Therapy* Massachusetts Association for Occupational Therapy

CORRIDOR

A *Diseases of the Biliary Tract* The Lahey Clinic Exhibitors Department of Surgery

B *Nutrition* Massachusetts Department of Public Health

Technical Exhibits

BALLROOM

BOOTH NO

Abbott Laboratories	22
Alkalol Company	14
American Hospital Supply Corporation	40
Artra Cosmetics Inc	49
The Baker Laboratories	39
Billhuber-Knoll Corporation	41
Ernst Bischoff Company Inc	24
The Borden Company	20
Brewer and Company	9 and 10
Burroughs Wellcome & Co (U S A), Inc	31
Cambridge Instrument Company, Inc	4
Cimel Cigarettes	15 and 16
Campbell & Ray Corporation	46
Cerufied Milk Producers Association	S-1
Ciba Pharmaceutical Products Inc	S-5
Crosbie-Macdonald	13
Davies, Rose & Company Ltd	47
Mrs Day's Ideal Baby Shoe Co	2
Devereux Schools	S-3
The Doho Chemical Corporation	56
Dy Dee Service Children Incorporated	12
J H Emerson Company	S-13
C B Fleet Co Inc	51
General Electric & Ray Corporation	26
Gerber Products Company	29
J E Hanger Inc	61
Hanover Chemical and Manufacturing Company	8
H J Heinz Company	7
Horlick's Malted Milk Corporation	S-4
The Junket Folks	36
Kellogg Company	S-6
Lederle Laboratories, Inc	45
Lee DeForest Laboratories	28
Liebel-Flütschheim Company	32
Eli Lilly and Company	50
M & R Dietetic Laboratories Inc	25
E F Mahady Company	37 and 38
Massachusetts Hospital Service Inc (Blue Cross)	6
Massachusetts State Pharmaceutical Association	43
Mead Johnson & Company	58 and 59
The Medical Protective Company	30
Mellin's Food Company of North America	35
The Mennen Company	34
T J Noonan Company	S-12
Parke Davis & Company	S-2
The E L Patch Company	23
Pet Milk Sales Corporation	S-7
Petrogalar Laboratories Inc	1
Philip Morris & Co, Ltd Inc	52
Picker & Ray Corporation	19
Randall Fauchney Corporation	S-9
Thomas W Reed Company	S-14
Riedel-de Haen Inc	S-11
S M A Corporation	5
Sanborn Company	21
Sandoz Chemical Works Inc	44

Schering Corporation.....	48
G. D. Searle & Company.....	S-8
Sharp & Dohme, Inc. ....	55
Smith, Kline & French Laboratories .....	53
E. R. Squibb & Sons.....	33
Standard X-Ray Sales Corporation.....	11
The Sun-Ray Company.....	17
Surgeons' and Physicians' Supply Company ..	60
Tailby-Nason Company.....	27
Trixie Corporation .....	3
White Laboratories, Inc. ....	42
Winthrop Chemical Company, Inc. ....	54
John Wyeth & Brother, Inc. ....	57

### LADIES' PROGRAM

Mrs. Frank R. Ober, *General Chairman*

**Tuesday, May 26**

**Registration.** 9:00 a.m.-5:00 p.m.

MEZZANINE FLOOR, HOTEL STATLER

**Reception and Tea.** 3:30 p.m.

SALLE MODERNE, HOTEL STATLER

**Dinner.** 7:30 p.m.

THE COPLEY-PLAZA

*Tickets on sale at Registration Desk*

**Wednesday, May 27**

**Registration.** 9:00 a.m.-12:00 m.

MEZZANINE FLOOR, HOTEL STATLER

**Luncheon.** 1:00 p.m.

WOMEN'S CITY CLUB OF BOSTON, 40 BEACON STREET

*Tickets on sale at Registration Desk*

### ANNUAL GOLF TOURNAMENT

The annual golf tournament of the Massachusetts Medical Society will be held at the Commonwealth Country Club, 91 Algonquin Road, Chestnut Hill (Newton), on Monday, May 25. The Burrage Bowl, the Society's championship trophy for the lowest net score, and other prizes for both net and gross play should stimulate interest in this tournament. Play will begin at 1:00 p.m. The greens fee for 18 holes is \$2.00; for two or more rounds, \$2.50. For additional information, communicate with Mr. Robert St. B. Boyd, executive secretary, 8 Fenway, Boston (KEN 2094), or a member of the Golf Committee, which is composed of the following: Dr. Roy J. Heffernan, Chairman, Dr. Edward A. Cooney, Dr. Thomas E. Dinan, Dr. Allan L. Davis and Dr. Roger T. Doyle.

### COMMITTEE ON POSTGRADUATE INSTRUCTION

A luncheon meeting of the district chairmen of the Committee on Postgraduate Instruction will be held on the fourth floor of the Hotel Statler on Wednesday, May 27, at 12:30 p.m. (Inquire at information desk for the room number.)

### MASSACHUSETTS MEDICO-LEGAL SOCIETY

A meeting of the Massachusetts Medico-Legal Society will be held on the fourth floor of the Hotel Statler on Tuesday, May 26, at 2 p.m. (Inquire at information desk for the room number.)

### DEATHS

**BALDAUF**—LEON K. BALDAUF, M.D., of Waltham died April 30. He was in his sixty-fifth year.

Dr. Baldauf received his degree from Johns Hopkins University School of Medicine in 1905. He became a member of the faculty of Albany Medical College and later served as professor of pathology and bacteriology University of Louisville School of Medicine. He had recently been appointed professor of pathology at Middlebury University School of Medicine. He was a member of the Massachusetts Medical Society and the American Medical Association.

His widow survives him.

**BARNES**—FRANCIS J. BARNES, M.D., of Cambridge died April 28. He was in his eightieth year.

Born in Newton, Dr. Barnes received his degree from Harvard Medical School in 1888. From 1916 to 1926 was chief of staff of the Cambridge City Hospital. He was a member of the Massachusetts Society of Examining Physicians, and was a fellow of the Boston Medical Library, the Massachusetts Medical Society and the American Medical Association.

He is survived by his widow, a daughter and two grandchildren.

**BENSON**—CHARLES S. BENSON, M.D., of Haverhill died April 30. He was in his seventieth year.

Born in Lewiston, Maine, Dr. Benson received his degree from Columbia University College of Physicians and Surgeons in 1896. He had practiced surgery in Essex County for many years and was the head of the Benson Hospital. Dr. Benson was vice-chairman of the medical advisory board of District No. 4, Selective Service System, and had served as a draft-board physician during World War I. He was a former president of the Essex North District Medical Society, and was a fellow of the American College of Surgeons, the Massachusetts Medical Society and the American Medical Association.

**CELCE**—FRANK F. CELCE, M.D., of Holyoke, died April 28. He was in his seventy-fifth year.

A native of Germany, Dr. Celce received his degree from University of Pennsylvania School of Medicine in 1893. He was a member of the Massachusetts Medical Society and the American Medical Association.

A son and a daughter survive him.

**DAMON**—ARTHUR L. DAMON, M.D., of North Woburn, died April 30. He was in his seventy-fifth year.

Born in West Cummington, Dr. Damon received his degree from University of Vermont College of Medicine in 1890. He was a fellow of the Massachusetts Medical Society and the American Medical Association.

His widow, a brother and a sister survive him.

**DURGIN**—EDWARD C. DURGIN, M.D., of Marshfield died April 26. He was in his sixty-fifth year.

Dr. Durgin received his degree from Tufts College Medical School in 1901. He was a former member of the Massachusetts Medical Society and the American Medical Association.

(Notices on page xii)

# The New England Journal of Medicine

Copyright, 1942, by the Massachusetts Medical Society

VOLUME 226

MAY 14, 1942

NUMBER 20

## THE DIFFERENTIAL DIAGNOSIS OF ACUTE APPENDICITIS AND ACUTE GASTROENTERITIS IN COLLEGE MEN\*

THOMAS B. QUIGLEY, M.D.† AND ANDREW W. CONTRATTO, M.D.‡

CAMBRIDGE, MASSACHUSETTS

ANY addition to the enormous and exhaustive literature of appendicitis requires some sort of apology. The present study was undertaken to clarify somewhat, if possible, the usually simple, but occasionally very difficult, differential diagnosis between acute appendicitis and acute gastroenteritis. Every practitioner of experience has at times been faced with the problem presented by the following case:

CASE 1 C. P., a 20-year-old undergraduate, first presented himself for treatment about 48 hours after the onset of an illness characterized by nausea, vomiting, mild mid-abdominal pain and diarrhea. The temperature was 96°F., and the abdomen was quite normal. The white-cell count was 30,800. The patient was advised to remain in his quarters, to eat a light diet and to return the next day. Twenty-four hours later, he stated that he felt better. The nausea and vomiting had ceased, but the abdominal pain persisted. The temperature was 99.4°F., and the white-cell count was 32,100. An experienced surgeon saw the patient at that time and noted nothing abnormal on examination of the abdomen other than rather loud, vigorous peristalsis. Furthermore, there was nothing remarkable on rectal examination.

The next day, the 4th day of the illness, the symptoms were unchanged, but there was for the first time diffuse abdominal and rectal tenderness. Operation was advised and agreed to. A ruptured pelvic appendix was found and removed. Convalescence was rather stormy, and 7 weeks later another laparotomy was carried out for intestinal obstruction. The patient missed, in all, 42 days of classes.

With the possibility of such near tragedy in the background, the surgeon may choose to operate in a doubtful case and, after removing a normal or "slightly injected" appendix, console himself with the thought that the most serious possibility has been ruled out and the patient is certain to recover. Although there will probably always be a small number of cases in which a correct diagnosis

cannot be established without laparotomy, it is a rather heroic diagnostic procedure, and in college men at least, it may have far-reaching effects, as illustrated by the following case:

CASE 2 S. J., an 18-year-old college freshman, was awakened from sleep by crampy, fairly constant, lower abdominal pain and nausea. The pain continued through the morning and became localized in the right lower abdominal quadrant. There were several loose watery bowel movements. At the time of examination, in the mid-afternoon, the temperature was 101.4°F., and the white-cell count 15,000. Spasm, tenderness and slight rebound tenderness were present in the right lower abdomen. There was moderate, diffuse rectal tenderness. Three experienced surgeons independently examined the patient, and each advised immediate operation for acute appendicitis.

At operation, 10 hours after the onset of the illness, a "scarred" but otherwise normal appendix was removed. No other abnormality was found on exploration. Convalescence was uneventful, and the patient resumed his classes 24 days later.

This boy's illness occurred at the beginning of his first period of college examinations. He was an industrious though not brilliant student and was enabled to attend college only by the grant of a scholarship. To keep the scholarship, he had to achieve honor grades in the examinations. Arrangements were made for him to take these in the hospital, the first on his fifth postoperative day. Fortunately, he did well, and was able to continue his college career. Needless to say, had he failed, his whole career might have been changed.

\* \* \*

The records of 100 cases of acute gastroenteritis and 60 cases of appendicitis occurring in Harvard University undergraduates between 1938 and 1941 were studied. In almost every case, the patient was seen by some member of the staff of the Department of Hygiene within twelve hours of the onset of the illness. All those with gastroenteritis were treated at the Stillman Infirmary. Only those cases of appendicitis were included in which operation

\*Read at the Clinical Congress of the American College of Surgeons, Boston, November 27, 1941.

†Instructor in surgery, Harvard Medical School, surgeon, Department of Hygiene, Harvard University, junior associate in surgery, Peter Bent Brigham Hospital.

‡Assistant in medicine, Harvard Medical School, physician, Department of Hygiene, Harvard University.

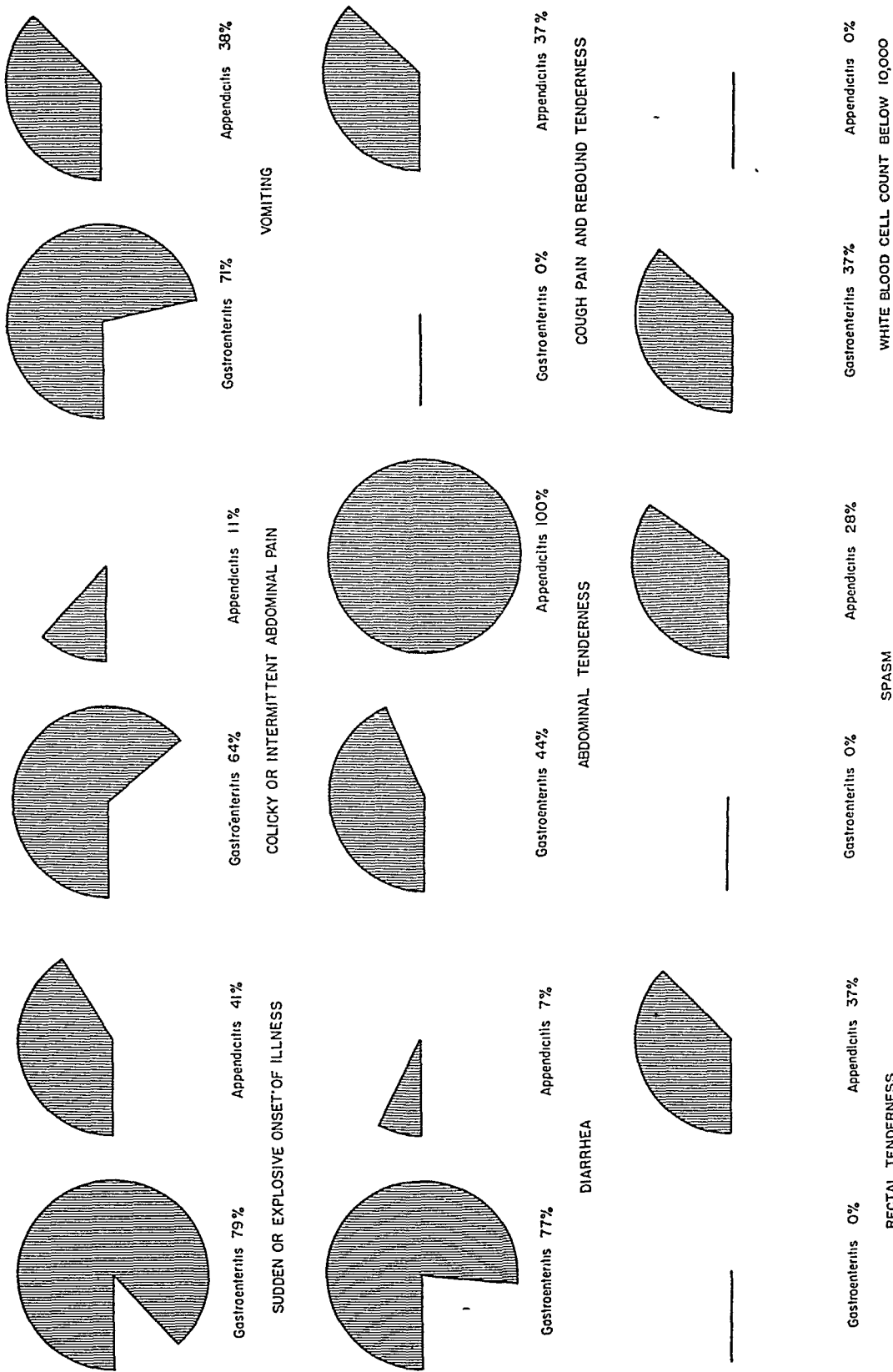


FIGURE 1.

had been carried out at a Boston hospital affiliated with the Harvard Medical School, and in which the pathologist's diagnosis agreed with the surgeon's and was unquestionably acute appendicitis. No deaths occurred in either series. The average time absent from classes for the patient with gastroenteritis was two days—for those with appendicitis, twenty days.

The records were studied with certain points in the history, physical examination and data from the laboratory in mind: the onset of the illness, whether explosive or insidious; the character and location of the abdominal pain; the presence or absence of nausea, vomiting, diarrhea and chills; the degree of fever and leukocytosis; and the presence or absence of abdominal spasm and tenderness.

The results are best described with reference to each of the signs and symptoms studied.

#### *Onset of Illness*

A sudden or explosive onset was more characteristic of gastroenteritis, occurring in 79 per cent, whereas in 59 per cent of the cases of appendicitis the onset was gradual or insidious (Fig. 1).

#### *Severity of Pain*

An attempt was made to classify the degree of abdominal pain as mild, moderate or severe, although such pain is admittedly difficult to evaluate and involves personal variations in sensitivity. Aside from the fact that 19 per cent of the patients with gastroenteritis had no pain whatever, no significant differences were found in the two groups. In 49 per cent of the appendicitis and 79 per cent of the gastroenteritis cases, the pain could be classified as mild. Severe pain was found in only 3 per cent of the appendicitis series.

#### *Character of Pain*

Steady abdominal pain occurred in 89 per cent of the appendicitis cases, whereas 64 per cent of the patients with gastroenteritis who had pain described it as colicky or intermittent.

#### *Localization of Pain*

Of the patients with appendicitis, 24 per cent described their pain as diffuse or general; 8 per cent placed it in the upper abdomen and 68 per cent in the lower abdomen. More than twice as many patients with gastroenteritis, or 58 per cent, were unable to localize the pain; 28 per cent described it as occurring in the upper abdomen, and only 12 per cent in the lower abdomen.

#### *Vomiting*

Vomiting occurred almost twice as often in the cases of gastroenteritis—in 71 per cent, as compared with 38 per cent in the appendicitis series.

#### *Diarrhea*

As might be expected, 77 per cent of the patients with gastroenteritis complained of diarrhea. Loose, repeated bowel movements occurred in only 4 cases of appendicitis, and 2 of these patients had taken cathartics. Ten other patients with appendicitis who had taken cathartics failed to develop diarrhea. In a review of the records, the value of closely questioning the patient on this point became apparent. Often, he states that he has had diarrhea, when actually there have been only one or two somewhat loose bowel movements.

#### *Chills*

Although often mentioned as an important diagnostic point, true chills did not occur in either series.

#### *Hyperperistalsis*

The presence of loud, rapid borborygmi was described in 44 per cent of the cases of gastroenteritis and 10 per cent of the cases of appendicitis, roughly paralleling the occurrence of diarrhea.

#### *Tenderness*

Mild tenderness was present in 44 per cent of the cases of the gastroenteritis group: 26 in the lower abdomen, and 18 above the umbilicus. Every patient with appendicitis exhibited some degree of abdominal tenderness when examined. In only 1 case was it above the umbilicus; in 2, it was described as equal in both lower quadrants, and in the remaining 95 per cent it was confined to the right lower quadrant. Cough pain and rebound tenderness were present in 37 per cent and were of great diagnostic significance, occurring in none of the cases of gastroenteritis. Rectal tenderness was also confined to the patients with appendicitis, occurring in 37 per cent. It was noted repeatedly that strain of the abdominal muscles associated with vomiting and retching can produce a superficial sort of tenderness and even slight voluntary spasm. As a rule, however, this is confined to the upper abdomen and is not elicited with the patient fully relaxed.

#### *Spasm*

The evaluation of abdominal spasm is at best difficult in its early stages, but it is of significance that it was described in 28 per cent of the patients with appendicitis and in none of those with gastroenteritis.

#### *Fever*

The average temperature for the cases of gastroenteritis was 99.1°F., and for the appendicitis group 98.8°F. It is perhaps significant that although 9 per cent of the former exhibited temperatures of



more than 101°F. by mouth, only 1 in the latter group was recorded.

#### *White-Cell Count*

The average white-cell count was a little higher for appendicitis: 18,300 as compared with 12,400 for gastroenteritis. Of greater consequence was the finding that none of the appendicitis cases had a white-cell count of less than 10,000, whereas 37 per cent of the gastroenteritis series did.

\* \* \*

Although, as a rule, the diagnosis is clear and straightforward between gastroenteritis and appendicitis, in the exceptional and bizarre cases the following diagnostic points appear to be worthy of consideration.

An explosive onset, colicky abdominal pain, vomiting, diarrhea, high fever and a white-cell count

below 10,000 and bizarre or absent abdominal signs appear to be characteristic of gastroenteritis.

An insidious onset and a steady abdominal pain, on the other hand, favor the diagnosis of appendicitis. Tenderness and true spasm are of the greatest importance, and rebound or cough tenderness referred to the right lower abdominal quadrant is almost pathognomonic.

#### SUMMARY

Attention is called to the urgency of a correct differential diagnosis between acute gastroenteritis and acute appendicitis in college men.

The symptoms, signs and laboratory data in 100 cases of acute gastroenteritis and 60 cases of proved appendicitis are reviewed, and the significant differences summarized.

## COLLES'S FRACTURE: A STUDY OF X-RAY FILMS BEFORE AND AFTER REDUCTION\*

JAMES W. SEVER, M.D.†

BOSTON

THIS study is an effort to determine, by means of roentgenograms, what should constitute a satisfactory anatomic reduction following a Colles's fracture. Measurements of the degree of deformity of the distal fragment of the radius in relation to the long axis of the shaft before and after reduction were made. X-ray interpretations by the roentgenologist were checked and occasionally discarded as unreliable and optimistic, in relation to the actual anatomic findings. It is obvious from this study that surgeons and roentgenologists need further care and instruction in methods of satisfactory reduction of such fractures and in the more careful interpretation that should be offered in any given case by study of the plate. Strict consideration of the normal anatomic relations should always be the criterion by which a good or unsatisfactory reduction is reported to the surgeon. This study does not undertake to report on the functional results, which are to be reported in a later paper in which the anatomic findings will be correlated with the functional results so far as possible.

In this report, 199 cases of Colles's fractures were studied, and so far as the x-ray films were available before and after reduction, measurements

were made from them. In each plate, a line was drawn parallel to the long axis of the radius in the lateral plane, and another line was drawn parallel to the plane of the radiocarpal joint. Then, with a transparent protractor, the joint angle was determined in relation to the long axis of the radius. In this way, an excellent and fairly accurate determination of the amount of the original deformity or displacement of the distal radial fragment and of the relative degree of replacement following reduction was obtained.

A few degrees one way or the other must be allowed for error in such measurements. In many cases, the angle of rotation of the forearm varied, but the roentgenologist assured me that this rotation would not alter to any great extent the joint angle as I determined it, so long as it was a reasonable attempt at a lateral view.

There were 40 men and 159 women in this series. The right wrist was fractured in 89 cases and the left in 112 cases; the ulnar styloid was fractured in 84 cases. There was a great variety in the types of fractures noted—from the simple fracture of the lower end of the radius, often without much displacement, to the severe comminuted fractures, with considerable displacement of the fragments in all directions. No attempt is made in this report to classify them further, since such a classification would be useful only for two rea-

\*Read at the annual meeting of the New England Surgical Society, Hanover, New Hampshire, September 5, 1941.

†Assistant professor of orthopedic surgery, Harvard Medical School, associate surgeon, Orthopedic Service, Children's Hospital, chief surgeon, Orthopedic Service, Cambridge Hospital.

sions—namely, an anatomic one, and one having to do with function in relation to the types of fracture. These factors will be considered in the later report on function. No cases of reverse

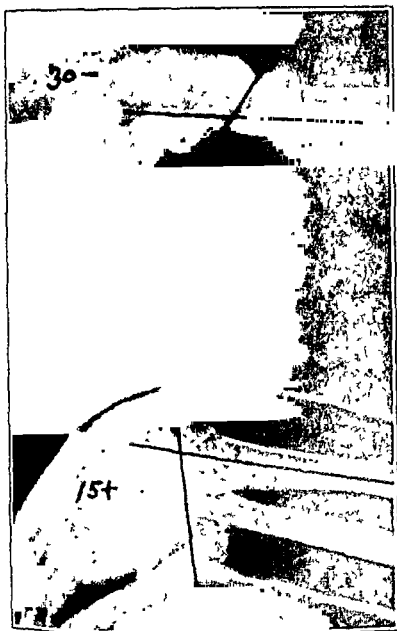


FIGURE 1.

*These films show excellent reduction, however, the postreduction view is not a true lateral*

Colles's fracture or the so-called "Smith fracture" were seen in this series.

An average of 181 cases showed the degree of deformity, or backward rotation of the radiocarpal joint before reduction, to be  $-28^\circ$  from the perpendicular. Ten cases had an average of  $7.8^\circ$ , which is about half normal. The normal forward palmar inclination of the radiocarpal joint to the long axis of the radius averages about  $15^\circ$  beyond the right angle; that is, the joint, with the hand pronated, faces distinctly downward to allow for full and free flexion. All measurements noted in this report are, however, to be considered plus or minus, in relation to a right angle, to the long axis of the shaft of the radius. In the anteroposterior view, the concave articular surface of the radius faces inward at an angle of about  $25^\circ$ . Following reduction, a number of patients had no check-up films, so that data regarding a satisfactory reduction could not be obtained.

In patients on whom check-up x-ray studies were made, it was found that 36 cases were reduced to only  $90^\circ$ , and 24 cases had an average residual deformity, after reduction, of  $-8.3^\circ$ . In other words, these 60 cases, or approximately 39 per cent, were not at all satisfactorily reduced. In 92 other postreduction cases, the average angle was determined as  $+10.9^\circ$ , which, for an average, was fairly satisfactory, but individual cases varied from  $+5^\circ$  to  $+30^\circ$ .

Besides these evident poor reductions of the gross backward deformity, often with persistence of the typical silver-fork appearance, there was a marked lapse in correction of the radial deviation of the hand. In this way, and because of the lack of correction of these two primary and major fac-



FIGURE 2

*This case had considerable prereduction deformity, which was not wholly corrected.*

tors, it was evident that the main problem of reduction of the fracture had not been grasped.

Fractures that had been reduced by surgeons of experience and skill generally showed an excellent anatomic result. In the other cases, there were many lapses, owing, I believe, to lack of knowledge

of what had actually happened, and how to correct it adequately.

For many years, Colles's fractures have been regarded as simple fractures, which anyone could treat, and this point of view has been emphasized by the rather loose teaching of a number of men who should have known better. All that was necessary, it was stated, was a simple, single motion of flexion of the wrist following breaking up of the impaction of the radius. Adduction of the hand was not insisted on as a means not only of restoring length to the radius but also of re-establishing the relation of the radioulnar joint. As a result, flexion of the wrist in plaster, following an attempted reduction, has been all that has been

ing of the distal radial fragment has not been wholly reduced. Wrist flexion has become the position in which it has been assumed that the fracture has been satisfactorily reduced, when that is often not true. The hand is generally only pulled on and the wrist flexed, without any real attempt to manipulate and reduce the radial fragment. Ade-

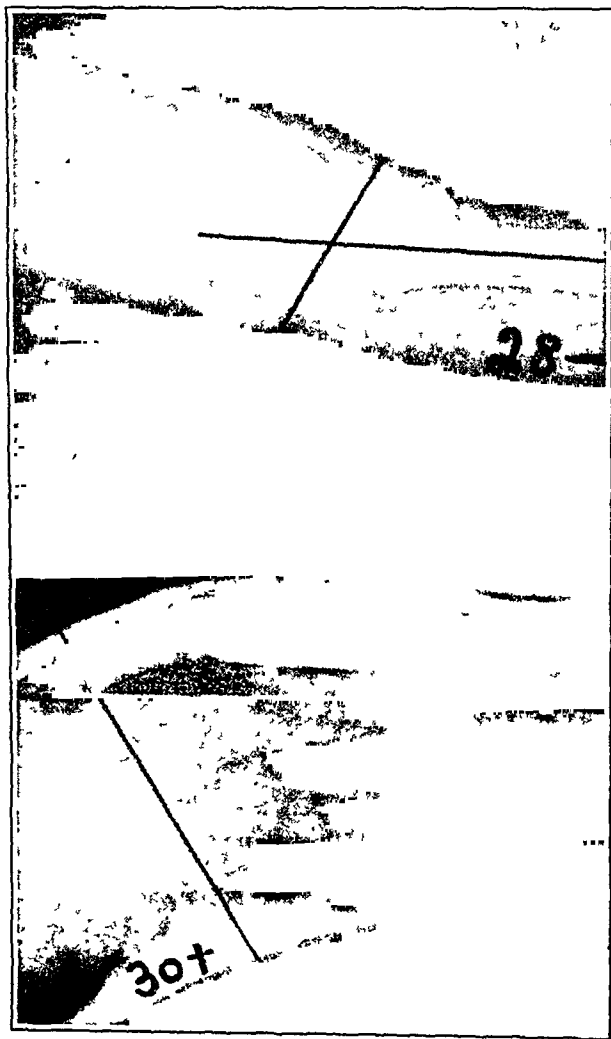


FIGURE 3.

*In this case, there was excellent reduction, even though the postreduction film is not a true lateral.*

done in many cases. In this study of x-ray films, I have seen many in which the wrist is only moderately flexed—the motion occurring at the radio-carpal joint, but limited, because the backward tilt-

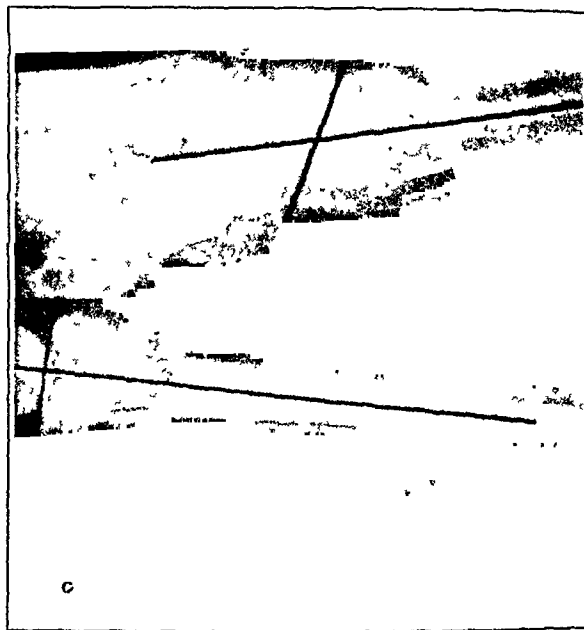


FIGURE 4.

*These films show a bad deformity that was corrected to a right angle only; the reduction was excellent.*

quate reduction of the backward angulation of the radial fragment is not accomplished—or rarely so—by flexion of the wrist alone. Flexion and adduction of the wrist should be only secondary positions, following adequate reduction of the fracture itself, and merely to prevent recurrence of the deformity.

In my opinion, there is no one and universal method by which a Colles's fracture may be easily and successfully reduced, but certain procedures, such as loosening of the impaction, flexion of the backwardly rotated distal fragment and adduction of the hand, are essential. In part, I believe, this complacent attitude has been the result of the lack of knowledge on the part of the physicians in interpreting the x-ray films, and of the optimism of the roentgenologist in reporting "good position" or "satisfactory reduction following manipulation" when such a report should never have been made. In many of these cases, there has been only slight reduction, if any, of the rotation of the distal radial fragment, and very little consequent restoration of the normal joint angle. This, I believe, is the fault of both the surgeon and the roentgenolo-

gist and is due to ignorance and faulty observations on the part of both. A proper measurement of the

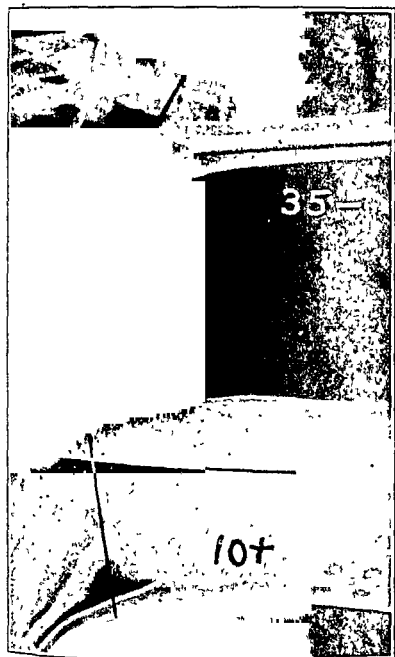


FIGURE 5.

*In this case, there was a badly comminuted fracture, in which all the carpal bones were in front of the long axis of the radius; an excellent reduction was obtained*

displacement before and after reduction should be part of the x-ray record and should be so reported.

321 Dartmouth Street

#### DISCUSSION

Dr OTTO J. HERMANN (Boston): The first thing I should like to mention is the use of the term "Colles's fracture." I have instructed my interns not to use that designation or "Pott's fracture" as a final diagnosis. When such general terms are used, they should be followed by an anatomic description of the fracture.

Several years ago, in an excellent paper, Dr. Grantley W. Taylor described the different types of Colles's fracture. Seventy-five per cent are the ordinary type, and in my estimation, their care is very simple. It is the comminuted types, which disturb the integrity of the radio-ulnar joint, in which poor results are obtained. I have seen cases in which the comminuted fractures have been well reduced that have gone on to a poor end result because they were taken care of in the ordinary routine manner. For this reason, I try to get the intern to de-

scribe the fracture in an anatomic fashion, and in that way the man handling it afterward knows with what he is dealing, and whether or not a case may need the necessary protracted fixation and to be kept up in flexion and pronation longer than the average case.

Haggard, in a rather good paper on this subject, advocated prolonged fixation. It was not clear to everyone what he was driving at, but I think it was at complicated types.

In treating these fractures, I tell my men to be sure to reduce the radial end and then pay attention to the ulna, which is the chief point after the radial fracture is reduced. The position we generally use is pronation flex-

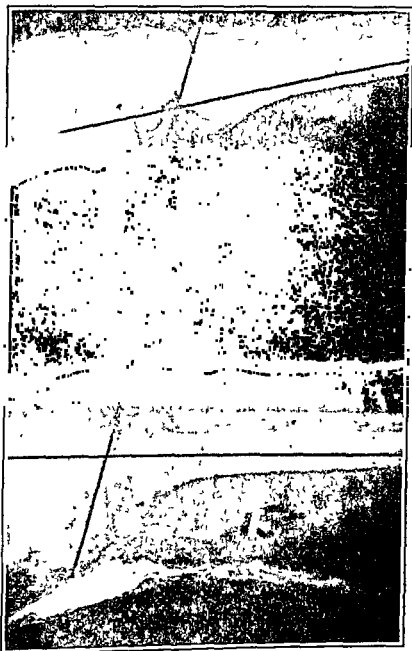


FIGURE 6.

*These films show poor and incomplete reduction; the hand was flexed, but the radial fragment was still displaced and rotated backward.*

tion, attention being paid to the ulna, getting good deviation and keeping the ulna up and in.

Dr. PIERCE H. LEAVITT (Brockton, Massachusetts): The subject of Colles's fracture is still a controversial one. Surgeons were fighting over it in the good old days, and they are still fighting about it; there is still not enough emphasis on proper attack.

If a patient with gall-bladder disease or a goiter becomes worse, it is usually accepted by relatives and friends that these are serious cases and that the patients do not do very well, and the matter is ended. A Colles's fracture, however, especially with those of us who

meet it every two or three weeks of our lives, is a walking advertisement and not a very good one, if things do not go well.

Out in the country, where we meet the young lads who have come out of the big hospitals where they have had their training, we find a rather poor job done on Colles's fractures. The first thing seems to be that they lack the

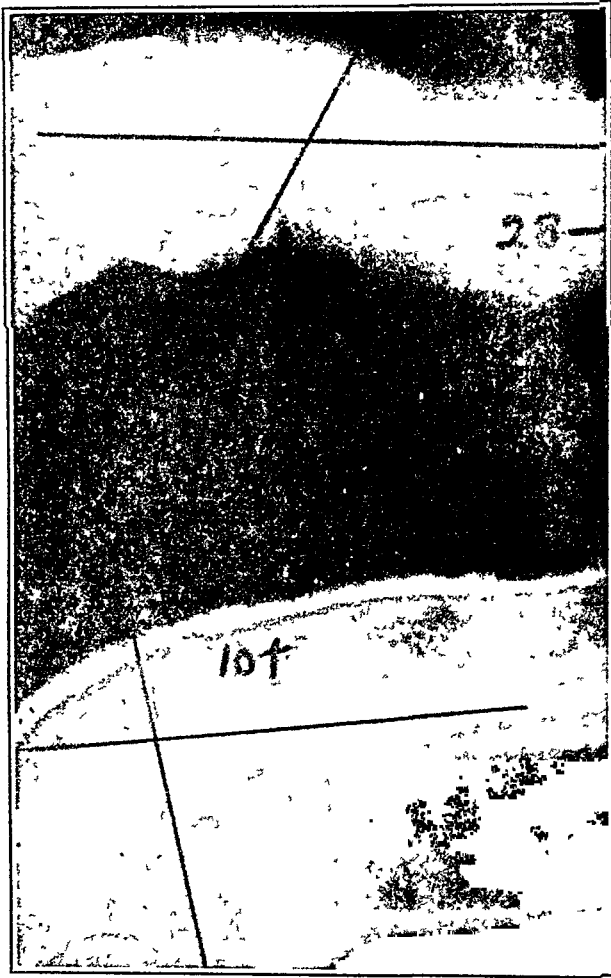


FIGURE 7.

*In this case, excellent reduction was obtained; note that both films are true lateral views.*

courage to go ahead and take hold of the fracture and reduce it. They take it in hand, fool around a bit and put splints on and get somebody to take an x-ray film, and in six or eight weeks, the case drops into the hospital and the fracture is incompletely reduced.

I think more instruction should be given to the interns on nonfracture services; it should be emphasized that a Colles's fracture is a very grave thing and that it takes a definite amount of skill to handle one properly, and they should be carefully instructed on how to do so. There is a tendency for the intern to call up and say, "There is a Colles's fracture in," and the visiting man says, "All right, go ahead and fix it up"; they do it and get away with it in about 75 per cent of the cases, but the remaining 25 per cent are poorly done. I should put up a plea, being out in the country, for more careful, really severe, instruction and caution to the young lads in the handling of what everybody calls a simple fracture but to my mind is not.

DR. JAMES B. WOODMAN (Franklin, New Hampshire): I should like to ask Dr. Sever if he ever uses local anesthesia — novocain — in the reduction of Colles's fracture.

It has been my observation that these fractures are largely impacted and that complete relaxation makes it very much easier to reduce the fracture and get it where it will stay; it seems to me that the majority, after once being fully and completely reduced, have a tendency to stay reduced, although there are some that do not.

I used a local anesthetic once and got away with it, in an old lady. I did not wish to give her anything more than a local anesthetic.

DR. EZRA JONES (Manchester, New Hampshire): Dr. Sever has very well covered the subject of the usual type of Colles's fracture, and brought out the interesting points: proper forward angulation of the articular surface of the lower end of the radius and proper x-ray films. I thought it might be of interest to report two cases of an unusual type of this fracture, the reverse Colles's or Smith type. This, as you know, is very difficult to hold after reduction.

In one of these, when the patient came to the hospital, the fracture was reduced and placed in flexion, as the ordinary Colles's fracture is. There was a marked deformity two days later. After the next reduction, it was placed in moderate dorsiflexion. This resulted in a forward angulation of the lower fragments. After the next attempt, reduction was accomplished, and a cast was applied with the forearm and hand at 120°, but deformity resulted. Then it was decided that an open reduction was necessary.

This time, an incision was made over the dorsum of the forearm, and a screw was placed from the shaft down into the lower end. This gave a satisfactory result and, I believe, is an excellent way to hold this particular type of fracture.

DR. SEVER (closing): I used a local anesthetic once, at the suggestion of Dr. Robert Carruthers, of Cincinnati, who used to come to Boston occasionally. He and his son are very great advocates of local anesthesia in the reduction of fractures of all types. In this one case, a fractured wrist, I did not use novocain enough to anesthetize the area completely and I did not succeed in doing what I wanted to very comfortably. I did not like the method, and I have never used it in the reduction of a Colles's fracture since.

I use gas and oxygen or pentothal sodium, which is very simple and very easy, and in that way one can obtain sufficiently long anesthesia to do anything that one chooses.

I was very much interested in Dr. Jones's cases of reverse Colles's or Smith fracture, because I have never seen one. I have been looking for one for a long time, and here he shows up with two.

There was a very interesting paper, during the last year, in the *Journal of the American Medical Association*, on Smith fractures, in which the authors said that no case of reverse Colles's fracture could be held, or satisfactorily reduced and held, without an open reduction and fixation by some means or other. After hearing Dr. Jones's cases, I think that is probably quite right.

I do believe that we should make an effort to see that the x-ray technicians take true lateral views and insist on it, or even go and be present when the films are taken, and then make adequate measurements of the joint angles. It is a simple and satisfactory procedure, and one knows where one stands.

## ESSENTIAL DYSMENORRHEA\*

MAURICE FREMONT-SMITH, MD†

BOSTON

**E**SSENTIAL dysmenorrhea is a medical enigma, and the last sixty years have done little to solve this problem. In 1879, Dr J. M. Duncan, of St Bartholomews, discussed both the etiology and treatment of this disorder in terms almost identical with those in current use today.

The condition, although not serious in itself, may result in severe economic, social and psychologic handicapping of a young woman forced to look forward month after month to hours or days of regularly recurring pain and periodic disorganization of life. Small wonder that some women fear and resent their function as women and pass on to their adolescent daughters a distorted attitude toward the specific biologic function of womanhood.

It is to point out how little is known concerning the pathogenesis of dysmenorrhea that this paper is presented. Some recent investigative work is reviewed, contradictory experimental conclusions are presented, and the consequent confusion in rationale of treatment is discussed.

The onset of dysmenorrhea may coincide with the menarche or may first appear after months (even a few years) of painless menstruation. The pain, sometimes severe, crampy and usually suprapubic (occasionally with radiation to the back and thighs), may begin a few hours before and continue through the period, or twenty-four to forty-eight hours previously, ceasing with the appearance of active bleeding. Nausea and prostration are not infrequent.

Pregnancy usually (although not always) cures the condition; dilatation of the cervix gives relief, sometimes permanent, and presacral neurectomy eliminates pain (with an occasional failure and an occasional recurrence). Scores of remedies, some of physiologic potency, many inert, have given temporary relief.

Numerous theories have been offered in explanation of this condition.

## MECHANICAL THEORIES

For years, *cervical obstruction* was believed to be the cause of dysmenorrhea, and this hypothesis was sustained by the fact that dilatation was so frequently followed by relief. It is now recognized that, although a rare case of menstrual pain is due to cervical obstruction, such pain is not, strictly speaking, essential dysmenorrhea. In essential dysmenorrhea, the cervix is often soft and patu-

lous.<sup>1,2</sup> Why relief follows dilatation is not understood — paralysis of parasympathetic nerve endings in the cervix has been suggested. The degree and duration of relief is apparently related to the degree of dilatation obtained and the length of time it is maintained. Such relief rarely persists over six months, after which pain frequently returns at its previous level of intensity. The fact that even temporary relief is obtained after cervical dilatation, however, focuses attention on the cervix as a possible source of pain in this condition.

*Hypoplasia of the uterus* is present in some women who experience pain with the periods,<sup>2</sup> and long continued estrin therapy has lessened, but not cured, dysmenorrhea in a few cases.<sup>3</sup> Meigs<sup>4</sup> finds soft and atonic, as well as small, firm and anteverted, uteri in women with this disorder. He has noted many in whom the uterus is normal in size and consistence. The rhythm, ovulation and ability to bear children in women suffering from dysmenorrhea are characteristically normal.

*Presacral neuritis* has been considered a cause of dysmenorrhea. Davis<sup>5</sup> states:

in the majority of cases of severe spasmodic dysmenorrhea the peripheral sympathetic nerves of the uterus — as represented by the presacral nerve — are pathologically altered in some degree. This alteration is in the direction of a subacute or chronic neuritis, and manifests itself in widespread degeneration of the ganglion cells, interstitial infiltration, and the other changes described in detail above.

Such changes were found in over 70 per cent of his cases.

*Psychologic factors* are of undoubted importance in the etiology of dysmenorrhea.† Novak and Harnik<sup>6</sup> believe that all cases are explainable on the basis of psychic trauma. These authors report 168 cases treated by psychotherapy, with complete relief in 71 and improvement in 89. Others consider a lowered psychologic threshold responsible for dysmenorrhea, thus, stimuli of normal intensity, originating in the uterus, are interpreted, at the psychic level, as pain.<sup>7</sup>

That the pain of dysmenorrhea is in some way associated with *contractions of the uterine muscle* has been postulated on the following evidence: the pain is like that of uterine colic, it is described as identical with the pain of abortion by women who have experienced both, afterpains mimic the cramps of dysmenorrhea; during dysmenorrhea, the

\*Presented in part at the annual meeting of the American Clinical and Obstetrical Association, Skytop, Pennsylvania, October 17, 1941.  
†F. M. Smith, M.D., in Medicine, Harvard Medical School, associate physician at Massachusetts General Hospital.

‡A strong argument for a psychologic factor in dysmenorrhea is the response of patients to suggestion. Temporary relief follows almost every type of treatment with substances frequently contradictory in physiologic activity or else physiologically inert.

blood has been reported to leave the body in gushes<sup>5</sup>; and introduction of a sound into the uterine cavity produces identical pain.

Contradictory evidence exists, however, concerning the type of uterine motility obtaining throughout the normal menstrual cycle, and the causal relation between uterine contraction and pain. In the monkey<sup>8</sup> and, according to Dickinson,<sup>9</sup> in human beings, the greatest activity in the uterus and tubes occurs just prior to ovulation (in the normally menstruating woman between the fourteenth and sixteenth days of the cycle). With or soon after ovulation, these movements progressively decrease, and the latter part of the cycle is characterized by quiescence, persisting during corpus-luteum activity. During menstruation in human beings, Dickinson noted (by rectal palpation) only moderate contractility of the uterus—"never reaching an intensity comparable to that observed at the mid-interval."

Knaus<sup>10</sup> filled the cavity of the uterus with sterile oil and registered the changes in uterine pressure on a kymograph attached to an insufflator placed in the cervix. He found rhythmic contractions present during the first fourteen days of the cycle; during this period, the uterus responded by contraction to the intravenous injection of preparations of the posterior pituitary gland. From the sixteenth day to just before menstruation, spontaneous contractions were absent, and the uterus failed to contract following the intravenous injection of posterior pituitary extract. Knaus believed that the date of ovulation could be determined by the change in uterine response to pituitary extract.

However, Moir,<sup>11</sup> using the intrauterine balloon method, noted that myometrial activity was greater during the first and second days of menstruation than in any other portion of the cycle. When pain was present, the degree of uterine contraction roughly paralleled the intensity of discomfort experienced. In the presence of pain, he invariably found frequent and irregular contractions, during which intrauterine pressures of 120 mm. of mercury or more were observed. At the height of the cramp in many patients, the intrauterine pressure "exceeded by a considerable margin the systolic [?] brachial] blood pressure." Pain was experienced as the contraction neared its acme, but "tended to continue until the uterus was completely relaxed, and even then did not always cease at once." Moir reasoned that pain might be due, not to the uterine spasm as such, but to a diminution of blood flow during contractions, resulting in local ischemia of the myometrium. He suggested that the cramps were caused by a mechanism similar to that productive of pain in angina pectoris.

Other observations, however, cast doubt on a necessary relation between cramps and simultaneous uterine contractions. Falls et al.<sup>12</sup> stated that progesterin, given on the seventh day of the puerperium, effectively inhibited the uterine contractions associated with afterpains. Lubin, Clarke and Reynolds,<sup>13</sup> on the other hand, showed that although progesterin relieved the pains in every case in their series, the duration and frequency of contractions were not significantly altered. In cases in which lessening of amplitude of contraction occurred, relief of pain preceded recognizable changes in the height of contractions. Their conclusion was that "relief from after pains is not necessarily associated with striking changes in uterine motility."

Lackner, Krohn and Soskin<sup>2</sup> obtained complete relief of pain in 8 of 10 patients by endocrine treatment given during attacks of dysmenorrhea. In 5, relief followed progesterone therapy; in 3, progesterone was ineffective, and the pain was relieved following estrin. Two patients obtained no benefit from either preparation. Moreover, these authors, using the intrauterine balloon method, reported:

At least two of the women who obtained relief from progesterone showed no diminution in the size of their uterine contractions at the time their pain was completely relieved. The other three cases did show reduction in uterine motility, but relief occurred without amounts of progesterone necessary to cause demonstrable decrease in uterine contractions.

This work failed to establish the therapeutic value of progesterone in dysmenorrhea, and cast doubt on the hypothesis relating pain to uterine contractions per se.

Wilson and Kurzrok<sup>14</sup> confirmed Moir's observation that maximal contractions occur not just prior to ovulation but at the onset and during the early phase of menstrual flow. They found that the follicular phase was characterized by high tonus and small, rapid uterine contractions, and the luteal phase by lower tonus and slow contractions. They stated that "contractions of maximum intensity appear precisely when dysmenorrhea occurs." However, examination of seventy-two tracings (intrauterine balloon) from 14 patients with dysmenorrhea revealed "no significant variation in either tonus, rate or amplitude," as contrasted with three hundred and fifty-one tracings in 29 normal controls. They stressed the fact that only patients who had ovulated and showed a secretory endometrium could have essential dysmenorrhea.\*

Finally, Wilson and Kurzrok,<sup>7</sup> in 1940, studying 29 cases of dysmenorrhea by the intrauterine bal-

\*A woman with primary amenorrhea in whom cyclical bleeding was produced at regular intervals by the administration of estrin had painless periods. When progesterone was added to produce a secretory endometrium, the period was for the first time accompanied by pain.

loon procedure, failed to confirm Moir's finding that menstrual cramps coincided with unusually strong contractions of the uterus. Although dysmenorrhea was present, no apparent alteration from the normal myometrial motility was found. In each case in which pressures were recorded during cramps, the amplitudes were well below the level of the systolic pressure. In 1 patient, pituitary extract brought about an intrauterine pressure exceeding 120 mm., but no pain was experienced. If pain was already present, pituitary extract increased it, and uniformly caused a rise in tonus and an increase in amplitude and frequency of contraction. The authors reported one experiment in which the balloon was introduced into the uterus during dysmenorrhea; large contractions, typical of early menstruation, were observed. Later, the balloon was expelled. On its immediate reintroduction, no pain was experienced, but "except for a slight reduction in tonus [usual with introduction of a bag], there was no significant alteration in the type of contraction." Kurzrok believes, therefore, that "dysmenorrhea may be regarded as a disorder in which *normal* [italics mine] uterine contractions, during the phase of maximum amplitude, reach consciousness."

In summary, the following statements express these contradictory opinions concerning uterine physiology: uterine activity is greatest just prior to ovulation; the strongest uterine contractions occur at onset of menstruation; painful menstruation is accompanied by excessively strong contractions, resulting in high intrauterine pressures; progesterone relieves afterpain without simultaneously inhibiting contractions; there is no relation between cramps and the strength of uterine contractions or the height of intrauterine pressures; and dysmenorrhea does not occur in the absence of a secretory endometrium.

#### ENDOCRINE THEORIES

If the above observations are not in agreement regarding the physical mechanism of pain production, agreement is even less evident in the several endocrine theories proposed to explain dysmenorrhea. Fluhmann<sup>15</sup> lists the following current hypotheses: deficiency of estrin, excess of estrin, lack of progesterone, excess of progesterone, thyrotoxicosis, hypoglycemia and calcium deficiency. He remarks that dysmenorrhea may have no relation to a disturbed endocrine balance.

The various theories are not considered in this study except so far as they concern observations made in the Ovarian Dysfunction Clinic of the Massachusetts General Hospital.

Twenty-five cases of essential dysmenorrhea treated with estradiol benzoate were reported from this clinic in 1940 by Sturgis and Albright.<sup>3</sup> These

authors observed, confirming Kurzrok's findings, that ovulation during the preceding cycle was a prerequisite for dysmenorrhea. They demonstrated that by correctly timed administration of a potent estrogen, which acted presumably to inhibit the pituitary follicle-stimulating hormone and thus suppressed ovulation, painless bleeding could be consistently substituted for a painful period, and that such substitution could be continued over many months.

Although endometrial biopsy directly before a painful period invariably showed the normal secretory pattern, a proliferative endometrium was found prior to bleeding in every case in which a painless menstrual period had been induced by the administration of estrogens. Cramps could be induced in patients experiencing painless (anovulatory) bleeding by the administration of sufficient amounts of progesterone.

Since the publication of Sturgis and Albright's report, these observations have been verified and extended. Other estrogens, such as stilbestrol and estradiol dipropionate, have been substituted for estradiol benzoate, with identical results. In a few cases, estrogens given during the last two weeks of the cycle have brought about diminution—but in no case elimination—of cramps. Estrin therapy given approximately every other month over long periods (three years) has not, except in a few cases, brought about improvement in dysmenorrhea after therapy has been stopped. Progestin given to patients with dysmenorrhea during the week preceding the flow has generally increased pain at the subsequent period.

No satisfactory treatment for dysmenorrhea has been developed. Relief may be obtained by suppression of ovulation and production of conveniently timed anovulatory bleeding. As soon as normal menstruation, including ovulation, is resumed, dysmenorrhea recurs.\*

In a regular twenty-eight-day cycle, pituitary action may be consistently inhibited,—that is, ovulation may be suppressed,—and estrin-withdrawal bleeding, which is invariably painless, may be produced at about the usual time of the next expected period by one of the following procedures: about 15 mg. of estradiol benzoate intramuscularly on the sixth day following onset of the period, and every third day thereafter to a total of six doses; 1 mg. of diethyl stilbestrol orally on the sixth day after onset, and daily over a total period of twenty days; and 10 mg. of estradiol dipropionate intramuscularly on the sixth and sixteenth days following the onset of the period. If the

\*That pituitary function may be inhibited over long periods, with immediate resumption of activity after the inhibiting influence is withdrawn, is evidenced by cases of granulosa cell tumor and arrhenoblastoma. Following removal of such tumors, normal ovulatory periods are resumed.



cycle is other than twenty-eight days, estrin treatment, to repress ovulation, should be started on the twenty-second day before the next expected period.

### DISCUSSION

Contractions of the uterus may be painless—even strong contractions, as at the onset of labor or, in a painless phase, following the administration of pituitary extract. In dysmenorrhea, however, considerable evidence of a time relation between uterine contractions and the occurrence of pain has been presented. Under certain circumstances, particularly when pituitary extract is given during a painful phase, both contractions and pain are increased simultaneously. For the existence of such a painful phase, the effect of progesterone is apparently necessary.

Therefore, the following tentative conclusions seem warranted: the pain of dysmenorrhea does not occur in the absence of active uterine contractions; and one or more secondary factors must be present if pain is to occur. If this is true, treatment of the disorder could be effective either by causing diminution of uterine contractions or by influencing this unknown secondary factor. One may thus regard the contraction as the precipitating and some other (? endocrine or circulatory) factor as the predisposing cause of dysmenorrhea.

### SUMMARY

Theories of the causation of dysmenorrhea are reviewed, contradictory observations on normal uterine physiology are presented, and the present status of treatment is discussed.

12 Hereford Street

### REFERENCES

1. Novak, E., and Reynolds, S. R. M. The cause of primary dysmenorrhea: with special reference to hormonal factors. *J. A. M. A.* 99:1466-1472, 1932.
2. Lackner, J. E., Krohn, L., and Soskin, S. The etiology and treatment of primary dysmenorrhea. *Am. J. Obst. & Gynec.* 34:248-266, 1937.
3. Sturgis, S. H., and Albright, F. The mechanism of estrin therapy in the relief of dysmenorrhea. *Endocrinology* 26:68-72, 1940.
4. Meigs, J. V. Personal communication.
5. Davis, A. Discussion on intrinsic dysmenorrhoea. *Proc. Roy. Soc. Med.* 29:931-947, 1936.
6. Novak, J., and Harnik, M. Ursache und Behandlung der Dysmenorrhoe. *Med. Klin.* 25:251-254, 1929. Die psychogene Entstehung der Menstrual Kolik und deren Behandlung. *Ztschr. f. Geburtsh. u. Gynäk.* 96:239-296, 1929.
7. Wilson, L., and Kurzrok, R. Uterine contractility in functional dysmenorrhea. *Endocrinology* 27:23-28, 1940.
8. Westman, A. Untersuchungen über die Physiologie der Tuba uterine bei Macacus Rhesus-Affen. *Acta obst. et gynec. Scandinav.* 8:307-355, 1929.
9. Dickinson, R. L. The technic of timing human ovulation by palpable changes in ovary, tube, and uterus. *Am. J. Obst. & Gynec.* 33:1027-1033, 1937.
10. Knaus, H. Eine neue Methode zur Bestimmung des Ovulationstermines. *Zentralbl. f. Gynäk.* 53:2193-2203, 1929.
11. Moir, C. Discussion on intrinsic dysmenorrhea. *Proc. Roy. Soc. Med.* 29:950-952, 1936.
12. Falls, F. H., Lackner, J. E., and Krohn, L. Effect of progestin and estrogenic substances on human uterine contractions. *J. A. M. A.* 106:271-275, 1936.
13. Lubin, S., Clarke, F. J., and Reynolds, S. R. M. The relation of after-pains to uterine contractions following administration of progestin. *Am. J. Obst. & Gynec.* 33:143-149, 1937.
14. Wilson, L., and Kurzrok, R. Studies on the motility of the human uterus in vivo: a functional myometrial cycle. *Endocrinology* 23:79-90, 1938.
15. Fluhmann, C. F. Ovarian dysfunctions and their treatment. *J. A. M. A.* 116:831-836, 1941.

## MEDICAL PROGRESS

### LABORATORY AIDS IN THE DIAGNOSIS AND PROGNOSIS OF HEART DISEASE\*

LAURENCE B. ELLIS, M.D.†

BOSTON

THE average cardiac patient can be diagnosed with accuracy and treated properly and effectively with little or no assistance from the laboratory. Many patients, however, are not average and can be adequately evaluated only with the help of such laboratory aids, and since the total number of persons with real or suspected heart disease is very large, the total number of patients requiring such study will be very considerable. In general, laboratory tests of value in cardiology can be divided into those that give information concerning the pres-

ence of heart disease or one of its manifestations, and those that are useful in estimating the functional capacity of the heart. However, just as it is impossible to divide clinical symptoms or physical signs into those that are purely diagnostic and solely prognostic, so the two types of laboratory procedures often overlap. Moreover, some tests are sufficiently simple, accurate and helpful to be part of the armamentarium of the general practitioner; some are of established practical value but are complex or require elaborate apparatus so that they fall into the province of the specialist or the large clinic; and finally there are tests that may be usefully employed in research in cardiologic problems but have not yet become applicable in clinical practice. Every physician should know, to some extent at least, of the tests that fall into each group, and their bounds of usefulness.

Reprints of articles in this series are not available for distribution, but the articles will be published in book form. The current volume is *Medical Progress: Annual, 1940* (Springfield, Illinois: Charles C Thomas Company, 1941. \$4.00).

\*From the Thorndike Memorial Laboratory, and the Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

†Associate in medicine, Harvard Medical School; assistant physician, Thorndike Memorial Laboratory; assistant visiting physician, Boston City Hospital.

### Valuable Laboratory Tests in General Practice

**Electrocardiogram** When one thinks of a laboratory test in the diagnosis of heart disease, the first that comes to mind is undoubtedly the electrocardiogram. The application of the electrocardiogram to the general practice of medicine was dealt with in a previous progress report.<sup>1</sup> Since then, little that is new of importance to the general practitioner has been published, although a good summary of its value by Marvin<sup>2</sup> has appeared, as well as several good new textbooks, notably those by Graybiel and White<sup>3</sup> and Katz,<sup>4</sup> and new editions of older but standard texts, such as those by Ashman and Hull,<sup>5</sup> and Pardee.<sup>6</sup>

The place of the electrocardiogram in general practice should be evaluated in the light of the following facts. The electrocardiogram is an instrument for the measuring of changes in electrical potential set up in the heart by the spread of the excitatory impulse or the contraction of the heart muscle; it measures this and nothing else. It gives valuable information regarding arrhythmias and heart block; it is often of great diagnostic help in cases of myocardial infarction and frequently shows changes indicative of disease in the heart that are useful when assessed against the clinical findings. It gives no information directly of the presence of valvular disease and, hence, is of little help in the interpretation of murmurs. It reveals nothing regarding the presence or absence of myocardial failure, either congestive or anginal. With proper appreciation of the bounds of its usefulness, and adequate training in the interpretation of the tracings, it is a valuable and occasionally essential aid in the handling of cardiac patients. Unfortunately, there is at present a tendency on the part of some physicians not fully trained in electrocardiography to exploit it beyond its limitations, with the result that on occasion much harm is done from wrong diagnosis and ill-advised therapy based on the misinterpretation of electrocardiograms.

**Cardiac roentgenography.** The x-ray offers the best method of studying the size and shape of the heart and its various chambers and of the great vessels. Although an anteroposterior roentgenogram with the tube at a distance of 6 or 7 feet, to minimize distortion, is usually adequate, more information as a rule can be gained from fluoroscopic examination, which gives a dynamic picture of the movement of the various parts of the heart and great vessels, and more easily permits study in the oblique and lateral positions. Such study is particularly useful in estimating enlargement of the aorta, the left auricle or the right ventricle. Although no test is highly reliable, fluoroscopy is the most helpful method of detecting early syphilitic aortitis. The diagnosis of mitral stenosis can sometimes be confirmed by this procedure when

the results of physical examination are equivocal.<sup>7</sup> It has been claimed that myocardial infarctions can be detected by such examination<sup>8</sup>; however, few roentgenologists or cardiologists are sufficiently skilled in fluoroscopy to diagnose such lesions with certainty in the absence of other clinical evidence. Just as with electrocardiography, there is an unfortunate tendency for some to exaggerate the role of roentgenology in cardiac diagnosis.

Recently, Robb and Steinberg<sup>9</sup> have perfected a method, which had been previously employed, for the visualization of the heart and great vessels by the sudden introduction into the circulation of a large amount of opaque material (Diodrast) and the recording by x-ray photographs taken at appropriate times. This method has at times proved to be of great help, especially in the differential diagnosis of mediastinal lesions, but it is a procedure whose use is limited, owing to the great technical dexterity and experience required and to the fact that its safety has not yet been completely established.

**Vital capacity.** Ever since the demonstration by Peabody and his associates in 1917 of a reduced vital capacity of the lungs in congestive heart failure, this test, being simple and easy to carry out, has been widely employed. Unfortunately, it has a limited application in the diagnosis of individual patients. Although it is quite true that the vital capacity is reduced in early heart failure, the limits of normal are so wide that minor reductions may not be detectable; and, moreover, conditions that frequently enter into the differential diagnosis of heart failure, such as chronic pulmonary disease, often also involve a reduction in vital capacity. Occasionally, the demonstration of a normal vital capacity in a person who complains of great difficulty in breathing is evidence in favor of the functional nature of the complaint, but such patients with neurocirculatory asthenia not uncommonly register low vital capacities, possibly because of an inability properly to perform the respiratory maneuver involved in the test.

This test is most helpful in following the progress of individual patients with known heart disease, since an increase or decrease in the vital capacity is often a useful index of improvement or regression. However, the patient's own statements regarding the degree of dyspnea encountered in his daily activities are usually fully as accurate a guide of his condition.

**Velocity of blood flow.** The principle of this procedure was first applied on a large scale by Blumgart, who, in 1927, with the collaboration of Yens, devised the radioactive method. He<sup>10</sup> subsequently explored its significance, which he reported in a series of papers, in the preparation of most of which the late Dr. Soma Weiss was asso-

ciated. When a substance is introduced into a peripheral vein, it passes from there to the right heart, through the pulmonary circulation back to the left heart and out into the systemic arteries. If the arrival of such a substance, either in the pulmonary vessels or at some point in the systemic arterial system, can be determined, the speed of blood from the point of injection to the end point can be easily measured and related to normal standards obtained with the same technic. If the cross-sectional area of the vascular bed, especially in the lungs, does not change, changes in blood velocity will vary directly with changes in the output of the heart. There are, however, frequent changes in the cross-sectional diameter of the vascular bed, with or without alterations in the cardiac output. In heart failure, the blood velocity (or circulation time) is, with rare exceptions, prolonged owing either to pulmonary and peripheral stasis, with engorgement and widening of the blood vessels, or to a reduced cardiac output, or to both. There are rare cases of heart disease (hyperthyroid heart, severe anemia and, occasionally, beriberi) in which the circulation time may actually be fast even in the presence of congestive failure, because of peripheral vasodilatation or increase in cardiac output. In chronic pulmonary disease, the blood velocity is usually normal.

The chief practical value of blood-velocity determinations is in cases in which the cause of dyspnea (pulmonary or cardiac) is uncertain.<sup>11</sup> This problem most commonly arises in elderly people in whom the dyspnea may be due either to a failing arteriosclerotic heart or to senile emphysema and chronic bronchitis. In the former, the blood velocity may be prolonged; in the latter it is unchanged. Occasionally, the test may give helpful evidence regarding one of the rare types of heart disease with a rapid circulation mentioned above.

Finally, the test may be useful in detecting abnormal arterial shunts in congenital heart disease.<sup>12</sup> By the selection of appropriate substances, the appearance time can be determined either in the pulmonary vessels or in the systemic arteries after the passage of the pulmonary circulation. Naturally, the second involves a longer interval than the first. If, however, there is a right-to-left shunt in the heart, as with a patent interventricular septum with concomitant pulmonary stenosis (tetralogy of Fallot), the appearance time in the peripheral arteries may be as short as that to the lungs, owing to the short circuit.

Many substances are employed for the measurement of blood velocity, and the appearance time of each is registered in its own way — by quickened respirations, flushing, distinctive taste or burning sensation of the tongue, cough or the characteristic

odor of the breath. Radioactive material, sodium cyanide, decholin, calcium gluconate, saccharin and so forth are used to measure the circulation time through the lungs and to the systemic circulation, and ether and paraldehyde are employed as measures of the arm-to-lung velocity. Several articles summarizing the application and value of these various tests are available.<sup>10, 13</sup>

*Venous pressure.* The term "venous pressure" as applied to the study of heart disease refers to the pressure in the right auricle, which is obtained by determination of the pressure in a large peripheral vein and subtraction of whatever hydrostatic pressure difference there may be between the level of the vein and the estimated position of the right auricle.

There are two methods of estimating venous pressure, the direct and the indirect. One performs the indirect method by sealing a small transparent capsule over a superficial vein, usually of the dorsum of the hand, and increasing the air pressure within the capsule until the vein begins to collapse.<sup>14</sup> Although the procedure may still have some application in research, it is more involved, requires more experience and is less accurate than the direct method, which has largely supplanted it in clinical practice.

This latter method simply requires the cannulization of a vein with a large bore needle connected with a manometer filled with saline solution; one then relates the height of the column of fluid in the manometer to the level of the right auricle, as estimated from the dorsal<sup>15</sup> or ventral<sup>16</sup> surface of the chest.

In the majority of cases of heart failure, such a determination of venous pressure is unnecessary, since the diagnosis is sufficiently clear, or because a fairly accurate clinical estimate of the venous pressure can be obtained from observation of the level at which the external jugular veins collapse as the patient is gradually raised from a supine to a semi-recumbent position. However, it is occasionally difficult or impossible to tell whether edema is of cardiac origin or due to a noncardiac condition, such as portal or other venous obstruction. In such a case, the determination of venous pressure may be helpful, especially if carried out simultaneously above and below the suspected site of the obstruction — as in the cubital and femoral veins if obstruction of either the superior or inferior vena cava is suspected. Venous-pressure measurements may also be useful in following the progress of cardiac tamponade and as a guide for pericardial tapping.

*Arterial blood pressure.* The measurement of the arterial blood pressure is so universally employed that one hardly thinks of it as a laboratory

edure. However, certain refinements in the ng of blood pressure, although important, are oo easily overlooked, and every doctor would sell to review these as set forth in the state-<sup>17</sup> issued by the American Heart Association. raphic methods of recording blood pressure available but have not proved of great value imical practice.

**Hemoglobin determination.** No examination of tent suspected of heart disease is adequate out a hemoglobin determination to discover xistence of anemia, or rarely of polycythemia, ry or secondary. A hemoglobin determina-<sup>18</sup> carried out by an accurate method is sufficient, not necessary to perform a red-cell count is the hemoglobin content is abnormal<sup>19</sup> emia places a burden on the circulation in ways. On the one hand, diminution in the<sup>20</sup> globin, and hence of the oxygen carrying r of the blood, results in impaired nutrition<sup>21</sup> the heart because of relative anoxia of the<sup>22</sup> ardiu; on the other hand, the heart of the<sup>23</sup> ne person attempts to compensate for the low<sup>24</sup> en capacity of the blood by increasing its out<sup>25</sup> and hence the work of the heart is increased<sup>26</sup> y, anemia alone leads to heart failure, much<sup>27</sup> commonly, anemia of mild or moderate de-<sup>28</sup> exists as an aggravating burden in a person<sup>29</sup> organic heart disease. Such anemia can<sup>30</sup> ly be satisfactorily treated, the added burden<sup>31</sup> ved and the patient's cardiac status thus im-<sup>32</sup> d.

ce the symptoms and signs of severe anemia<sup>33</sup> some resemblance to those of heart failure,<sup>34</sup> too frequently patients with normal hearts<sup>35</sup> ing from anemia are wrongly treated as cir-<sup>36</sup> pitients. These patients may complain of<sup>37</sup> hlessness, fatigue and dependent edema. They<sup>38</sup> have enlarged hearts with systolic and rarely<sup>39</sup> clic murmurs, and may exhibit electrocardio-<sup>40</sup> ic abnormalities. Such mistaken diagnoses<sup>41</sup> usually be easily avoided if proper examin-<sup>42</sup> of the blood is made.

**Sedimentation rate and leukocyte count.** Both<sup>43</sup> procedures have a useful place in cardiology,<sup>44</sup> ally when patients with active rheumatic<sup>45</sup> or myocardial infarction are followed. In<sup>46</sup> : rheumatic fever, either test is contributory<sup>47</sup> nce in favor of activity.<sup>48</sup> The sedimentation<sup>49</sup> is likely to be elevated for a much longer<sup>50</sup> than the leukocyte count and hence is a<sup>51</sup> : guide of persistence of the infection,<sup>52</sup> ough neither test is infallible. In myocardial<sup>53</sup> tion, the leukocyte count is often elevated<sup>54</sup> n the first twenty-four to forty-eight hours,<sup>55</sup> e time of the febrile response that generally<sup>56</sup> s, and may reach 20,000 to 25,000. Within<sup>57</sup> days, it usually returns to normal. The sedi-

mentation rate does not begin to rise, as a rule,<sup>58</sup> for several days after the onset but continues<sup>59</sup> elevated in most cases throughout the healing<sup>60</sup> period—that is, about six weeks. It is the best<sup>61</sup> laboratory guide of healing in myocardial infar-<sup>62</sup> tion.<sup>63</sup>

**Blood nonprotein or urea nitrogen.** In cardio-<sup>64</sup> renal cases with organic renal insufficiency, in<sup>65</sup> marked heart failure when there is a depression of<sup>66</sup> renal function due to congestion, and in certain<sup>67</sup> patients who are dehydrated,—even occasionally<sup>68</sup> in the presence of edema,—azotemia may occur,<sup>69</sup> and its existence can be demonstrated by the find-<sup>70</sup> ing of an elevated blood urea nitrogen or non-<sup>71</sup> protein nitrogen. The toxic effect may contribute<sup>72</sup> to the heart damage and thus institute a vicious<sup>73</sup> circle. If this state of affairs is diagnosed, fre-<sup>74</sup> quently by the judicious administration of fluids,<sup>75</sup> much can be done to ameliorate it.

Tests that indicate early impairment of renal<sup>76</sup> function are often useful and provide guides to<sup>77</sup> the best management of certain difficult cases. A<sup>78</sup> simple test of this type, easily carried out in the<sup>79</sup> office or home, is the concentration test. If a<sup>80</sup> person can concentrate his urine to 1 020 or higher<sup>81</sup> after being deprived of water for fifteen to twenty-<sup>82</sup> four hours, his renal function is rarely greatly<sup>83</sup> impaired. If such a patient has, at the same time,<sup>84</sup> nitrogen retention, it is of extrarenal origin and<sup>85</sup> not due to renal insufficiency. Of course, if a<sup>86</sup> patient is edematous, and especially if he is in a<sup>87</sup> diuretic phase, it may be impossible to dehydrate<sup>88</sup> him sufficiently to obtain a concentrated urine sam-<sup>89</sup> ple, and under such circumstances the concentra-<sup>90</sup> tion test becomes of no help. Another renal-func-<sup>91</sup> tion test easily performed is the fractional phenol-<sup>92</sup> sulfonphthalein excretion test.<sup>93</sup> More compli-<sup>94</sup> cated, but more accurately quantitative, are the<sup>95</sup> various clearance tests, in which the rate of ex-<sup>96</sup> cretion of substances such as urea, creatinine,<sup>97</sup> inulin, Diodrast and glucose are determined.<sup>98</sup>

**Urine and blood sugar.** Since diabetes is so<sup>99</sup> commonly associated with degenerative vascular<sup>100</sup> disease, many cardiac patients also have diabetes.<sup>101</sup> The proper regulation of the diabetic state is an<sup>102</sup> important element in the therapy of heart disease.<sup>103</sup> Therefore, the urine of every cardiac patient<sup>104</sup> should be carefully and often repeatedly examined<sup>105</sup> for sugar, and if any sugar is found in the urine,<sup>106</sup> studies of the blood sugar level should be under-<sup>107</sup> taken.

**Serologic tests for syphilis.** It is universally<sup>108</sup> agreed that no clinical examination is complete<sup>109</sup> without a serologic test for syphilis, especially in<sup>110</sup> cardiac diagnosis, since a positive test may be the<sup>111</sup> only clue leading to a more extensive search for<sup>112</sup> early aortitis. A negative test cannot, however, be<sup>113</sup> considered proof of the absence of cardiovascular

syphilis. The reported incidence of patients with such involvement who have positive blood Wassermann reactions varies from 65 to 95 per cent. McDermott et al.<sup>23</sup> found only 2.2 per cent of a series of 135 patients with syphilitic aortitis who did not have either a positive Wassermann or a previous history of syphilitic infection or anti-syphilitic treatment. The number in whom the blood Hinton reaction, or a similar more delicate test, is negative is probably less, although statistical studies are not yet available.

*Plasma proteins.* The significance of plasma proteins has been fully discussed in other articles of this series.<sup>24, 25</sup> Plasma proteins, and especially plasma albumin, may be lowered in heart failure for any one or a combination of five reasons: deficient protein in the diet; deficient absorption of protein from the gastrointestinal tract; impaired formation of plasma albumin in the liver or elsewhere; loss of protein through the kidneys or in serous effusion; and hydremia. A low plasma protein, with resultant low plasma osmotic pressure, may therefore become a significant contributory factor in the edema of heart failure, although it is not the primary causative factor. Whenever persistent edema in heart failure does not respond to the usual therapy, it is useful to have a determination made of the plasma proteins or, better yet, of the albumin and globulin fractions. If the total proteins fall below 5.0 to 5.5 gm. per 100 cc., or if the albumin falls below 2.5 gm., the edema is probably in part maintained by low osmotic pressure. Not infrequently, under such conditions, the feeding of a high-protein diet proves beneficial.

Plasma proteins can be determined by direct chemical means without great difficulty, and clinical laboratories are now usually equipped to perform such tests. A simple way of estimating the total plasma protein is by measurement of the plasma specific gravity, which varies directly with the protein content. Relatively inexpensive and simple apparatus for such measurement is available.

*Blood culture.* The chief occasion for carrying out this procedure is in cardiac patients in whom acute or subacute bacterial endocarditis is suspected. These conditions are not uncommon. Repeated positive blood cultures are the greatest aid to accurate diagnosis, and since modern chemotherapy has in some cases proved highly beneficial, the value of establishing the correct diagnosis as early as possible is evident. If necessary, it is comparatively easy to obtain the blood for culture under sterile precautions in the home, and most hospitals and state health departments

are equipped to carry out the necessary bacteriologic examinations.

*Basal metabolic rate.* In heart failure, the basal metabolic rate, as obtained by the usual technic, often elevated to levels that average about 10 per cent above normal but may reach more than 50 or 60 per cent.<sup>26</sup> In the presence of heart failure, therefore, these determinations are of negative value only in excluding hyperthyroidism. However, the test is frequently of advantage in the differential diagnosis of certain types of cardiac syndromes, notably hyperthyroidism and neurocirculatory asthenia or menopausal symptoms.

#### *Specialized Laboratory Tests of Clinical Value*

*Phonocardiography.* Increasingly, instruments are being made available for the graphic registration of heart sounds and murmurs. Doctors are turning to such devices hoping that they will tell them what the human ear cannot hear. As often happens, they frequently expect too much. Phonocardiography is a specialized technic, still highly experimental and, like electrocardiography, requires special training in interpretation. Phonocardiographic recording devices are of various types ranging from those registering vibrations as they are produced, irrespective of the degree in which they are perceived by the human ear, to those modified that they register the vibrations in approximately the same fashion as that appreciated by the human brain. These devices have a considerable usefulness in the experimental laboratory or in exact clinical exploration, particularly in the study of heart sounds. At present, their use in the interpretation of murmurs is limited. Recent articles by Johnston and Kline<sup>27</sup> and by Rappaport and Sprague<sup>28</sup> discuss at length the factors that govern auscultation and the registration of sounds, whereas the most complete work on the graphic registration of human heart sounds in normal and pathologic conditions is the book by Orian and Braun-Menendez.<sup>29</sup>

*Blood volume.* Estimations of the blood volume are made indirectly by injection into the bloodstream of something that is mixed in the plasma without being excreted or destroyed in appreciable amounts for some time. Thus, if the amount injected, the concentration in the plasma and the rate of disappearance of the substance from the blood are known, the total circulating plasma volume can be calculated and, since the hematocrit is known, the blood volume as well. Inert dyes have been employed for this purpose since the demonstration by Keith, Rowntree and Geraghty<sup>30</sup> that vital red could be successfully employed for the purpose. Carbon monoxide<sup>31</sup> has also been employed to compute the circulating cell volume.

Inaccuracies in the earlier methods prevented the obtaining of many clinical data, but in 1935, Gregersen et al.<sup>3,2</sup> developed an improved modification of the dye method using Evans blue. Since then, much valuable information concerning blood-volume change in heart failure, as well as in other states, has been forthcoming, in large part in publications by Gibson and his associates.<sup>2,3,14</sup> They have confirmed the fact that the blood volume may be increased in congestive heart failure, often to a very significant degree. Although, in theory, determinations of the blood volume should be helpful in indicating the existence or extent of myocardial failure, practically, the test is so complicated that it is as yet applicable only in the research laboratory.

### Research Tests

**Cardiac output.** For many years, determinations of the cardiac output in human beings have been made in normal and abnormal states. Most of these have been carried out indirectly by the application of the Fick principle or by the rate of absorption through the lungs of foreign gases.<sup>30</sup> The Fick principle states that if the oxygen or carbon dioxide contents of the arterial blood and the venous blood returning to the heart are known and if the total oxygen consumption or carbon dioxide excretion per minute is also measured, the rate of blood flow can be easily calculated. The oxygen and carbon dioxide contents of the arterial and venous bloods are estimated from the gaseous contents of air from the lungs, obtained by special respiratory maneuvers. More recently, variations of this method have been widely used whereby foreign gases, such as nitrous oxide,<sup>30</sup> acetylene<sup>37</sup> and ethylolide,<sup>38</sup> are employed. If the rate of absorption of such gases from the lungs into the arterial blood is calculated and compared with the rate of oxygen absorption and the total minute oxygen consumption, the cardiac output can be readily computed. Such methods, and in particular that employing acetylene, when properly applied give reliable results comparable to the cardiac output measured directly by the obtaining of blood samples by direct puncture of the right heart and of the arteries.<sup>30</sup>

Through the application of such methods for estimating cardiac output, very valuable information has been gained concerning the abnormal physiology in heart disease and in heart failure. However, these techniques are not of use in the clinic, they are too complicated and require great skill by the operator and co-operation and training by the subject. Moreover, unfortunately, the very condition that is most essential to study—congestive heart failure—is that in which this test can be applied with the greatest difficulty or not at all.

**Arterial oxygen saturation.** It is now a comparatively simple procedure to obtain samples of arterial blood, determine its oxygen content and capacity and thus calculate the percentage saturation. This may be of value in any condition in which arterial anoxemia is suspected. The clinical sign, cyanosis, is brought about by an increased amount of reduced hemoglobin in the blood as it flows through the vessels that give skin color—namely, the venules.

Cyanosis may result from any one or a combination of a number of causes. In cardiac disease, two main factors may be responsible: arterial anoxemia and peripheral stasis. Normally, the blood is oxygenated as it leaves the lungs, and hence the arterial blood is about 95 per cent saturated with oxygen. This high degree of arterial oxygen saturation may be reduced by pulmonary factors, acute or chronic, that interfere with aeration of the blood (as in pulmonary congestion or consolidation, marked emphysema or pulmonary vascular disease), or by abnormal communications that permit blood to pass from the right side of the heart directly to the left side (as in some types of congenital heart disease).

Peripheral stasis, which occurs in some cases of mitral stenosis and in chronic right-sided failure or in venous obstruction, leads to cyanosis because of the slow blood flow and the unusual degree of oxygen unsaturation of the venous blood. The hemoglobin content of the blood markedly affects the development of cyanosis. Since this sign is dependent on the absolute amount of reduced hemoglobin in the peripheral blood, cyanosis cannot occur in severe anemia even though the factors that would ordinarily lead to it are present. Conversely, in polycythemia, cyanosis is often present even with normal arterial saturation and blood flow. The determination of the degree of arterial oxygen saturation in patients with polycythemia is an important differential test, since such saturation is essentially normal in primary polycythemia, whereas it is reduced in secondary polycythemia. Thus, on many occasions the determination of the cause of cyanosis in a given case is essential, and in such cases the estimation of arterial oxygen saturation becomes a desirable and often even a necessary procedure. At present, not many laboratories, outside research institutions, are equipped to carry out such determinations, but they are not especially difficult and no doubt will have wider clinical application in the future.

\* \* \*

No examination of any cardiac patient should be considered adequate without the performance of at least a few simple clinical tests. These are determination of the arterial blood pressure, hemoglobin

content of the blood, a serologic test for syphilis and a routine urinalysis. An electrocardiogram and roentgenographic study of the heart, although desirable for complete evaluation of the case, can often be dispensed with, but on occasion such procedures become absolutely essential to a correct diagnosis. Other laboratory procedures are often useful and sometimes necessary.

319 Longwood Avenue

## REFERENCES

1. Ellis, L. B. Electrocardiography in general medicine. *New Eng. J. Med.* 222:1078-1085, 1940.
2. Marvin, H. M. The use and abuse of the electrocardiogram in medical practice. *New Eng. J. Med.* 226:213-217, 1942.
3. Graybiel, A., and White, P. D. *Electrocardiography in Practice*. 319 pp. Philadelphia: W. B. Saunders Company, 1941.
4. Katz, L. N. *Electrocardiography including an Atlas of Electrocardiograms*. 580 pp. Philadelphia: Lea and Febiger, 1941.
5. Ashman, R., and Hull, E. *Essentials of Electrocardiography for the Student and Practitioner of Medicine*. Second edition. 373 pp. New York: Macmillan Co., 1941.
6. Pardee, H. E. B. *Clinical Aspects of the Electrocardiogram Including the Cardiac Arrhythmias*. Fourth edition. 434 pp. New York: Paul B. Hoeber, Inc., 1941.
7. Sosman, M. C. Subclinical mitral disease. *J. A. M. A.* 115:1061-1066, 1940.
8. Levene, G., and Lowman, R. M. Roentgen localization of myocardial damage resulting from coronary artery disease. *Radiology* 36:159-170, 1941.
9. Robb, G. P., and Steinberg, I. Visualization of the chambers of the heart: the pulmonary circulation and the great blood vessels in man: summary of methods and results. *J. A. M. A.* 114:474-480, 1940.
10. Blumgart, H. L. The velocity of blood flow in health and disease: the velocity of blood flow in man and its relation to other measurements of the circulation. *Medicine* 10:1-75, 1931.
11. Oppenheimer, B. S., and Hitzig, W. M. The use of circulatory measurements in evaluating pulmonary and cardiac factors in chronic lung disorders. *Am. Heart J.* 12:257-271, 1936.
12. Benenson, W., and Hitzig, W. M. The diagnosis of venous-arterial shunt by ether circulation time method. *Proc. Soc. Exper. Biol. & Med.* 38:256-258, 1938.
13. Kvale, W. F., and Allen, E. V. The rate of the circulation in the arteries and veins of man. I. Studies of normal subjects and of those with occlusive arterial disease and hyperthyroidism. *Am. Heart J.* 18:519-536, 1939.
14. Eyster, J. A. E. *The Clinical Aspects of Venous Pressure*. 135 pp. New York: The Macmillan Co., 1929.
15. Moritz, F., and v. Tabora, D. Über eine Methode, beim Menschen den Druck in oberflächlichen Venen exakt zu bestimmen. *Deutsches Arch. f. klin. Med.* 98:475-505, 1910.
16. Lyons, R. H., Kennedy, J. A., and Burwell, C. S. The measurement of venous pressure by the direct method. *Am. Heart J.* 16:675-693, 1938.
17. Committee for the Standardization of Blood Pressure Readings of the American Heart Association and the Committee for the Standardization of Blood Pressure Readings of the Cardiac Society of Great Britain and Ireland. Standard method for taking and recording blood pressure readings. *J. A. M. A.* 113:294-297, 1939.
18. Ellis, L. B., and Faulkner, J. M. The heart in anemia. *New Eng. J. Med.* 220:943-952, 1939.
19. Jones, T. D., Ham, T. H., and Massell, B. F. Round table discussion on sedimentation rate. *J. Pediat.* 12:675-688, 1938.
20. Riseman, J. E. F., and Brown, M. G. The sedimentation rate in angina pectoris and coronary thrombosis. *Am. J. M. Sc.* 194:392-399, 1937.
21. Chapman, E. M., and Halsted, J. A. The fractional phenolsulphonphthalein test in Bright's disease. *Am. J. M. Sc.* 186:223-232, 1933.
22. Talbott, J. H. Renal-function tests. *New Eng. J. Med.* 226:197-201, 1942.
23. McDermott, W., Tompsett, R. R., and Webster, B. Syphilitic aortic insufficiency: the asymptomatic phase. *Am. J. M. Sc.* 203:202-215, 1942.
24. Loeb, R. F. Plasma proteins in health and disease. *New Eng. J. Med.* 224:980-987, 1941.
25. Ellis, L. B. The causes and treatment of edema. *New Eng. J. Med.* 224:1060-1067, 1941.
26. Resnik, H., Jr., and Friedman, B. Studies on the mechanism of the increased oxygen consumption in patients with cardiac disease. *J. Clin. Investigation* 14:551-562, 1935.
27. Johnston, F. D., and Kline, E. M. An acoustical study of the stethoscope. *Arch. Int. Med.* 65:328-339, 1940.
28. Rappaport, M. B., and Sprague, H. B. Physiologic and physical laws that govern auscultation and their clinical application: the acoustic stethoscope and the electrical amplifying stethoscope and stethograph. *Am. Heart J.* 21:257-318, 1941.
29. Orías, O., and Braun-Menéndez, E. *The Heart Sounds in Normal and Pathological Conditions*. 258 pp. New York: Oxford University Press, 1939.
30. Keith, N. M., Rowntree, L. G., and Geraghty, J. T. A method for determination of plasma and blood volume. *Arch. Int. Med.* 16:547-576, 1915.
31. Chang, H. C., and Harrop, G. A., Jr. The determination of circulating blood volume with carbon monoxide. *J. Clin. Investigation* 5:393-405, 1928.
32. Gregersen, M. I., Gibson, J. J., and Stead, E. A. Plasma volume determination with dyes: errors in colorimetry: use of the blue dye T-1824. *Am. J. Physiol.* 113:54, 1935.
33. Gibson, J. G., 2nd, and Evans, W. A., Jr. Clinical studies on the blood volume. I. Clinical application of a method employing the azo dye "Evans Blue" and the spectrophotometer. *J. Clin. Investigation* 16:301-316, 1937. II. The relation of plasma and total blood volume to venous pressure, blood velocity rate, physical measurements, and sex in ninety normal humans. *Ibid.* 16:317-328, 1937. III. Changes in blood volume, venous pressure and blood velocity rate in chronic congestive heart failure. *Ibid.* 16:851-858, 1937.
34. Gibson, J. G., 2nd, and Evelyn, K. A. Clinical studies of the blood volume. IV. Adaptation of the method to the photoelectric microcolorimeter. *Ibid.* 17:153-158, 1938.
35. Harrison, T. R. *Failure of the Circulation*. Second edition. 502 pp. Baltimore: Williams & Wilkins Co., 1939. Pp. 126-147.
36. Krogh, A., and Lindhard, J. The volume of the "dead space" in breathing. *J. Physiol.* 47:30-43, 1913. The regulation of respiration and circulation during the initial stages of muscular work. *Ibid.* 47:112-136, 1913.
37. Grollman, A. *The Cardiac Output of Man in Health and Disease*. 325 pp. Springfield, Illinois: Charles C Thomas, 1932.
38. Starr, I., Jr., and Gamble, C. J. An improved method for the determination of cardiac output in man by means of ethyl iodide. *Am. J. Physiol.* 87:450-473, 1928.
39. McGuire, J., Hauenstein, V., and Shore, R. Cardiac output in heart disease: determined by the direct Fick method, including comparative determinations by the acetylene method. *Arch. Int. Med.* 60:1034-1042, 1937.

## MASSACHUSETTS MEDICAL SOCIETY

## PROCEEDINGS OF THE COUNCIL

Special Meeting, April 15, 1942

A SPECIAL meeting of the Council of the Massachusetts Medical Society was held in John Ware Hall, Boston Medical Library, 8 Fenway, Boston, on Wednesday, April 15, 1942, at 10:30 a. m.

Dr. Frank R. Ober, president of the Massachusetts Medical Society, presided and Dr. Michael A. Tighe served as secretary. There were 189 councilors present (Appendix No. 1).

The record of the February 4, 1942 meeting of the Council, as published in the *New England Journal of Medicine*, issue of March 12, 1942, was offered by the Secretary, who moved its adoption. This motion was seconded by Dr. I. R. Jankelson, Norfolk, and carried by vote of the Council.

Dr. Ober announced that the purpose of this meeting was to give consideration to the report of the Committee on By-Laws, appointed as the result of the action of the Council at its stated meeting in October, 1941. The personnel of this committee is as follows: Dr. J. Harper Blaisdell, chairman; Dr. Carl Bearse; Dr. John Fallon; Dr. Albert A. Hornor; and Dr. Harold R. Kurth.

Dr. Ober requested that the members observe the following regulations in debate so as to assure accurate reporting of the proceedings:

1. Changes in the text which are to be presented to the Council must be by way of amendment to that text.
2. Amendments must be in writing.
3. Written reference must be made to the chapter, section, page and line or lines amended.
4. The name of the councilor offering the amendment must be attached to it.

The President further requested that each councilor participating in the debate announce his name and district.

Dr. J. Harper Blaisdell, Middlesex East, was introduced. Dr. Blaisdell, preliminary to offering the report of his committee, paid tribute to Dr. Richard Dutton of Middlesex East. He said that it was due to Dr. Dutton's inspiration that this work was initiated. He added that his committee had held fifteen meetings involving at least one hundred hours and that many of these hours had been spent in conference with the Executive Committee and the standing committees involved in the contemplated changes. He thanked Dr. and Mrs. Kurth, of Methuen, Dr. and Mrs. John Fallon, of Shrewsbury, and Dr. and Mrs. Tighe, of

Lowell, for their hospitality. He expressed the thanks of his committee to Dr. Ober and Dr. Tighe for their help.

He reported that the legal aspect of the by-laws to be presented had been passed on by counsel, in the person of Mr. E. L. Twomey, and that the English had been checked by Dr. Robert N. Nye, managing editor of the *New England Journal of Medicine*. He called the Council's attention to the fact that the committee's report had not been signed by Dr. Albert A. Hornor, of Suffolk. He added that he would not infringe on Dr. Hornor's privilege of offering his own reasons for not doing so.

Dr. Blaisdell explained that after the text had gone to print, the necessity for certain typographical and textual corrections became evident. He said that these corrections did not involve any change in principle. He asked for the unanimous consent of the Council to make the following changes in the text:

That lines 14, 15 and 16\* of Chapter I, Section 5, be deleted. (These lines represent a repetition of what appears in Section 10 of the same chapter.)

That in line 15 of Chapter I, Section 9, "Chapter VII, Section 9, and Chapter VIII, Section 1," be substituted for "Chapter VIII, Section 9."

That Section 11 of Chapter I, which reads as follows:

Section 11. Committees having under consideration the applications of former fellows (a) whose resignations have been requested by the Committee on Ethics and Discipline or (b) who have been deprived of fellowship under the terms of Section 9 shall consult with the Committee on Ethics and Discipline before reporting their recommendations to the Council.

be deleted, and that the following be substituted:

Section 11. Former fellows who desire to be readmitted following (a) resignations requested by the Committee on Ethics and Discipline or (b) who have been deprived of fellowship under the terms of Section 9 shall make application in writing addressed to the Council and sent to the Secretary.

Such applications shall be referred for investigation to the board of membership of the district society concerned, which shall report with recommendations to the Committee on Membership.

The board of membership of the district society concerned and the Committee on Membership shall consult with the Committee on Ethics and Discipline before recommendations are reported to the Council.

The Council may readmit former fellows so recommended.

\* "Lines," whenever mentioned, refer to the copy of the proposed by-laws published in the April 2 issue of the *Journal*.



That in line 27 of Chapter VI, Section 1, "Chapter VII, Section 9," be substituted for "Chapter VIII, Section 1."

That in line 19 of Chapter VIII, Section 1, "Chapter VII, Section 9," be substituted for "Chapter I, Section 10."

On motion of Dr. Blaisdell and a second by Dr. Hilbert F. Day, Middlesex South, the Council gave unanimous consent to these changes.

Dr. Blaisdell moved that the report of this committee be accepted. The motion was seconded by Dr. Harold G. Giddings, Middlesex South, and adopted by vote of the Council.

Dr. Blaisdell moved that the Council proceed to consider the proposed by-laws chapter by chapter and section by section. This motion was seconded by Dr. Lester M. Felton, Worcester, and carried by vote of the Council.

Dr. Ober, anticipating a possible need, appointed Dr. Edward M. Halligan, Middlesex East, and Dr. Leroy E. Parkins, Suffolk, tellers.

There was some discussion at this point as to procedure. In this discussion the following councilors participated: Dr. George D. Henderson, Hampden, Dr. Raymond A. McCarty, Middlesex South, and Dr. Blaisdell. It was finally agreed that the vote would first come on the adoption of the section as contained in the text before the Council and, in the event that this section was adopted, a motion should be offered for the deletion of the corresponding section in the by-laws as amended in 1941.

Dr. Blaisdell offered Chapter VII, Section 1, which reads as follows:

## CHAPTER VII

### COMMITTEES

*Section 1.* Reports of committees containing recommendations that may require prolonged consideration shall be sent in abstract to the Secretary, at least six weeks before their presentation to the Council, for consideration by the Executive Committee and for publication in the official journal.

Every committee, annually on or before December 10, shall forward, to the chairman of the Committee on Finance, an estimate of its expenses for the ensuing fiscal year, which shall show the purpose of any proposed expenditure of \$100 or more and a similar detailed statement of its expenditures for the current fiscal year to and including November 30 with an estimate of expenditures for the current month of December.

All bills of \$100 or more incurred by a committee shall be countersigned by a majority of said committee and forwarded to the President for his approval.

All bills less than \$100 incurred by a committee shall be countersigned by the chairman of said committee and forwarded to the President for his approval.

Every committee shall render a written report to the Council at least once a year.

Dr. Blaisdell, in commenting on this section, said that it provides first, time for review by the Execu-

tive Committee of such committee reports and their publication in the *Journal* in advance of the Council meetings, as may require the mature deliberation of the councilors. Secondly, it provides that bills of \$100 or over must have the signature of all the members of a given committee. Dr. Blaisdell moved the adoption of Chapter VII, Section 1. The motion was seconded by Dr. William H. Allen, Bristol North.

Dr. John Homans, Suffolk, said that there was some question in his mind as to the ability of the Finance Committee to observe the timetable which was involved in this section.

Dr. Allen G. Rice, Hampden, asked if the chairman of the Finance Committee had had opportunity to be heard on this section. The answer was in the affirmative. The question was demanded. The motion was passed by vote of the Council.

Dr. Blaisdell moved that Section 11 of Chapter VII of the by-laws as amended in 1941 be deleted. This motion was seconded by Dr. John Fallon, Worcester, and adopted by vote of the Council.

Dr. Blaisdell read Section 2 of Chapter VII, which is as follows:

### COMMITTEES ELECTED BY THE DISTRICTS

*Section 2.* The Executive Committee of the Council shall consist of the President, President-Elect, Vice-President, Secretary and Treasurer and a councilor from each district society, chosen as provided in Chapter III, Section 5.

The Executive Committee shall meet at the call of the President. It shall assist the President in preparing matters for consideration by the Council.

It shall act on all questions of retirement, resignation, remission of dues, deprivation of fellowship for arrears, reinstatement following deprivation of fellowship for arrears, and transfer of fellows from one district to another without change of legal residence.

The Executive Committee may appoint and dismiss the Executive Secretary.

It shall authorize or confirm action by the officers in emergency.

The Executive Committee shall perform such other duties as the Council may require.

Dr. Blaisdell said that this chapter divides the committees of the Society into two groups, those elected by district societies and standing committees. It refers to the Executive Committee certain routine matters which heretofore had consumed considerable of the Council's time. Dr. Blaisdell moved the adoption of this section. The motion was seconded by Dr. John J. Curley, Worcester North.

Dr. David Cheever, Suffolk, questioned the wisdom of transferring to the Executive Committee the functions now resting in the Council and expressed himself as not being in favor of such a transfer. He said, however, that he was open to persuasion.

Dr. Walter G. Phippen, Essex South, thought that this was a fair disposition of the matters referred to in the section. He added, however, that the Executive Committee should be required to report its acts, as they pertain to this section, to the Council.

There was much discussion along the same lines. Those participating were Dr. Fallon, Dr. Allen G. Rice, Hampden, Dr. Richard M. Smith, Suffolk, and Dr. G. Colket Caner, Suffolk.

Dr. Ober at this point observed that the Executive Committee had reported at each meeting of the Council. There was a demand for the question. It was put and passed by vote of the Council.

Dr. Blaisdell moved the deletion of Section 10 of Chapter IV of the by-laws as amended in 1941. This motion was seconded by Dr. Jesse C. Hales of Worcester North and passed by vote of the Council.

Dr. Blaisdell presented Section 3 of Chapter VII. This section reads as follows:

*Section 3. The Committee on Public Relations shall consist of the President as chairman and one councilor from each district society, elected as provided in Chapter III, Section 5.*

*It shall concern itself with the relations between fellows of the Society and the public.*

Dr. Blaisdell moved its adoption. The motion was seconded by Dr. Frank H. Washburn, Worcester. It was adopted by vote of the Council without debate.

Dr. Blaisdell presented Chapter VII, Section 4. It reads as follows:

*Section 4. The Committee on Legislation shall consist of one fellow from each district society, elected as provided in Chapter III, Section 5.*

*It shall study, initiate and support measures to improve standards of medicine and promote the public welfare. It shall study and oppose such measures as it may deem contrary to the public welfare.*

*It may employ counsel, subject to approval of the President.*

*District legislative committees shall be auxiliary to and under the direction of this committee.*

Dr. Blaisdell moved the adoption of this section. The motion was seconded by Dr. Royal P. Watkins, Worcester.

Dr. Channing Frothingham, Suffolk, asked if the committee under this section had the power to set a precedent for the Society without referring the matter to the Council. He subsequently supplemented the question by asking as to whether or not under the section this committee would be permitted to go down to the State House and commit the Society.

Dr. Blaisdell answered that this committee will possess no other powers than those possessed by any other committee. He added, in substance,

that there might be times when this committee would be called on to act when a special meeting of the Council might not be feasible.

Dr. Ernest L. Hunt, Worcester, suggested that the Committee on Legislation might be stronger if the President of the Society were to designate the chairman or act as chairman himself.

Dr. Charles C. Lund, Suffolk, thought that a committee of eighteen scattered all over the State might be cumbersome. He added, however, that the committee could provide for its own executive committee. He added that the members of Middlesex South, Norfolk and Suffolk live within ten miles of the State House. He referred specifically to the line which reads, "It may employ counsel, subject to approval of the President" and said he did not understand its purpose.

Dr. Ober put the question and it was carried by vote of the Council.

Dr. Blaisdell moved the deletion of Section 6 of Chapter VII of the by-laws as amended in 1941. The motion was seconded by Dr. Curley and passed by vote of the Council.

Dr. Blaisdell presented Chapter VII, Section 5, which reads as follows:

*Section 5. The Committee on Nominations shall consist of one councilor, with another as alternate, from each district society, as provided in Chapter III, Section 5.*

*It shall nominate the officers and orator of the Society, and shall cause its report to be published in the notice of the annual meeting of the Council.*

He moved its adoption. This motion was seconded by Dr. John B. Hall, Norfolk. This motion was passed by the Council without debate.

Dr. Blaisdell presented Chapter VII, Section 6, which reads as follows:

#### STANDING COMMITTEES

*Section 6. The Committee on Arrangements shall consist of five fellows.*

*It shall be responsible for all arrangements for the annual meeting of the Society.*

*The chairman shall furnish the Secretary, on or before April 15, with all the data necessary for the annual program.*

*The secretary of this committee shall record its proceedings in a volume which shall be filed with the Secretary.*

Dr. Blaisdell moved the adoption of Chapter VII, Section 6. The motion was seconded by Dr. Richard M. Smith, Suffolk, and carried by vote of the Council.

Dr. Blaisdell moved the deletion of Chapter VII, Section 1, of the by-laws as amended in 1941. This motion was seconded by Dr. Allen H. Wright, Franklin, and carried by vote of the Council.

Dr. Blaisdell presented Chapter VII, Section 7, which reads as follows:

*Section 7.* The Committee on Publications shall consist of five fellows.

It shall supervise the publications of the Society.

It shall publish, when ordered by the Council, a directory of the officers and fellows.

It shall appoint the Shattuck Lecturer in accordance with the provisions of the Shattuck bequest.

It shall inform all readers of papers and discussers of the following rules:

All papers presented at the meetings of the Society shall be the property of the Society. No paper presented in the section meetings at the annual meeting shall occupy more than thirty minutes in its delivery. Each discussion shall be limited to five minutes, unless lengthened by vote of the meeting.

All papers shall be ready for publication, typewritten and accompanied by suitable material for illustrations, if any, when read to the sections or to the Society; and as soon as read they shall be handed to the secretary of the section or of the Society for transmission to the editor of the official journal.

Discussers shall correct and promptly return to the editor for publication, if deemed proper by this committee, the stenographer's transcribed notes of their remarks.

Dr. Blaisdell moved the adoption of this section. The motion was seconded by Dr. Richard M. Smith, Suffolk.

Dr. Fallon made a suggestion which he said emanated from Dr. Walter P. Bowers to the effect that the Committee on Publications would be a better body to select the annual orator than the Committee on Nominations.

Chapter VII, Section 7, was adopted by vote of the Council.

Dr. Blaisdell moved the deletion of Chapter VII, Section 2, of the by-laws as amended in 1941. The motion was seconded by Dr. I. R. Jankelson, Norfolk, and carried by vote of the Council.

Dr. Blaisdell presented Chapter VII, Section 8, which reads as follows:

*Section 8.* The Committee on Membership shall consist of five fellows.

It shall consider applicants applying for fellowship according to the provisions of Chapter V, Section 2c.

It shall consider matters relating to honorary or associate fellowship, retirement, resignation, remission of dues, deprivation of fellowship for any cause, reinstatement following deprivation of fellowship for arrears, transfer of fellows from one district society to another, as provided for in Chapter III, Section 3, and shall make recommendations to the Council or the Executive Committee, as provided in Chapter I, Sections 10 and 11.

This committee shall confer with the representatives of the supervising censors as provided in Chapter V, Section 1.

Dr. Blaisdell moved the adoption of Section 8. The motion was seconded by Dr. James P. O'Hare, Suffolk.

Dr. Eoline C. Dubois, Hampden, voiced a criticism of the section. Dr. Blaisdell answered and said that this criticism would be answered as the Council proceeded to consider other sections of the by-laws.

Section 8 was adopted by vote of the Council.

Dr. Blaisdell moved that Chapter VII, Section 3, of the by-laws as amended in 1941 be deleted. The motion was seconded by Dr. Charles J. Kickham, Norfolk, and adopted by vote of the Council.

Dr. Blaisdell presented Chapter VII, Section 9, which reads as follows:

*Section 9.* The Committee on Ethics and Discipline shall consist of five fellows.

It shall investigate and consider, either on charges submitted in writing or on its own initiative, any alleged or apparent offense on the part of any fellow, as provided in Chapter I, Section 9.

It shall either admonish him, request his resignation or report its findings to the President with its recommendations, if as a result of its investigations and after a hearing that has been requested by the fellow, the committee finds that he is guilty of such offense.

The President acting on such recommendations shall (a) censure the fellow, or (b) refer the matter to a board of trial, as provided in Chapter VIII, Section 1.

A member of the committee shall act as prosecuting officer in cases that come before a board of trial.

There was much discussion as to the implications involved in this section, Dr. Ralph R. Stratton, Middlesex East, Dr. Fallon, Dr. Kenneth L. MacLachlan, Middlesex East, Dr. Blaisdell, Dr. Cheever, Dr. Phippen, Dr. Charles J. Kickham, Dr. Rice, Dr. Smith, Dr. Lewis S. Pilcher, Middlesex South, Dr. Bearer, Dr. Shields Warren, Suffolk, and Dr. Maurice Fremont-Smith, Suffolk, participating.

Dr. Ober instructed Dr. Fallon, Dr. Rice, Dr. A. R. Gardner, Middlesex North, and Dr. Stratton to retire and bring in a new section which would relieve the difficulties that had been raised.

Dr. Blaisdell moved that action on Section 9 be postponed, pending the return of the above-mentioned group. The motion was seconded by Dr. Fallon and carried by vote of the Council.

Dr. Blaisdell presented Chapter VII, Section 10, which reads as follows:

*Section 10.* The Committee on Medical Education shall consist of five fellows.

It shall consider matters relating to medical education.

It shall annually revise, subject to approval by the Council, the list of recognized medical schools and colleges.

Dr. Blaisdell moved the adoption of Section 10.

Dr. Halbert G. Stetson, Franklin, asked as to whether or not the word "all" following the word "consider" would add strength to the section.

Dr. Leroy E. Parkins, Suffolk, asked as to whether or not it was proposed by this section that the Committee on Medical Education take

the place of the special Committee on Postgraduate Instruction. Dr. Ober answered, "No."

Dr. Stetson offered his suggestion as an amendment. This amendment was seconded by Dr. Fremont-Smith. The amendment did not prevail.

The original motion was adopted by vote of the Council.

Dr. Blaisdell moved the deletion of Chapter VII, Section 5, of the by-laws as amended in 1941. The motion was seconded by Dr. J. L. Chereskin, Hampden, and passed by vote of the Council.

Dr. Blaisdell presented Chapter VII, Section 11, which reads as follows:

*Section 11:* The Committee on Public Health shall consist of five fellows.

It shall foster the knowledge of the prevention and treatment of disease by any appropriate measures.

Dr. Blaisdell moved the adoption of this section. The motion was seconded by Dr. Hall. It was so ordered by vote of the Council without debate.

Dr. Blaisdell moved the deletion of Chapter VII, Section 7, of the by-laws as amended in 1941. The motion was seconded by Dr. Cheever and it was so ordered by vote of the Council without debate.

Dr. Blaisdell presented Chapter VII, Section 12, which reads as follows:

*Section 12.* The Committee on Medical Defense shall consist of five fellows.

It may appoint as auxiliary members one fellow in each district.

It shall act, under the provisions of the Medical Defense Act, on applications of resident fellows for legal services in the defense of suits for alleged malpractice.

It may take counsel with both plaintiff and defendant in threatened suits.

It shall report to the Committee on Ethics and Discipline any instance coming to its knowledge wherein a fellow, in connection with a suit for malpractice, has violated the code of ethics of the Society.

Dr. Blaisdell moved its adoption. The motion was seconded by Dr. Jankelson. Dr. MacLachlan asked if the words "It may appoint as auxiliary members one fellow in each district" were part of the by-laws of 1941. Dr. Ober answered in the affirmative.

Section 12 of Chapter VII was adopted by vote of the Council.

Dr. Blaisdell moved the deletion of Chapter VII, Section 8, of the by-laws as amended in 1941. The motion was seconded by Dr. Phippen and it was so ordered by vote of the Council.

At this point the committee appointed by Dr. Ober to shape up Chapter VII, Section 9, offered the following amendment to this section as written in the text: Insert after the words "a hear-

ing" the following: "of which the fellow has been duly notified."

Dr. Blaisdell moved the adoption of Chapter VII, Section 9, as amended. The motion was seconded and it was so ordered by vote of the Council.

Dr. Blaisdell moved the deletion of Section 4, of Chapter VII, of the by-laws as amended in 1941. The motion was seconded by Dr. Cheever and it was so ordered by vote of the Council.

Dr. Blaisdell presented Chapter VII, Section 13, which reads as follows:

*Section 13.* The Committee on Society Headquarters shall consist of five fellows.

It shall supervise the maintenance of the Society Headquarters.

It shall acquire funds for expansion, subject to approval by the Council.

Dr. Blaisdell moved the adoption of this section. The motion was seconded by Dr. Cheever and it was so ordered by vote of the Council.

Dr. Blaisdell moved the deletion of Section 9, Chapter VII, of the by-laws as amended in 1941. The motion was seconded by Dr. Curley and it was so ordered by vote of the Council.

Dr. Blaisdell presented Chapter VII, Section 14, which reads as follows:

*Section 14.* The Committee on Finance shall consist of five fellows.

It shall recommend to the Council, at the February meeting, the budget for the current fiscal year.

The budget shall show in detail the proposed expenditures and their allocation to the various officers, employees, committees, or any other person or persons authorized to expend the same, and shall make available to any fellow on request the purpose of any proposed expenditure of \$100 or more. The budget shall include for purposes of comparison similar items of expenditure for the previous year, if any.

It shall consider requests for extraordinary appropriations and shall refer them, with recommendations, to the Council for action.

It shall, at the close of the fiscal year after consultation with the Treasurer and with the approval of the Council, determine the amount to be refunded to the several district societies from the unexpended balance on December 31. This amount shall be apportioned among the district societies according to the number of annual assessments paid to the Treasurer before March 1.

Dr. Blaisdell moved the adoption of this section. The motion was seconded by Dr. Fallon. This section was adopted by vote of the Council without debate.

Dr. Blaisdell moved the deletion of Section 10 of Chapter VII of the by-laws as amended in 1941. The motion was seconded by Dr. Cheever and it was so ordered by vote of the Council.

Dr. Blaisdell presented Chapter VII, Section 15, which reads as follows:

*Section 15.* The Committee on Hospital Relations shall consist of five fellows.

It may appoint as auxiliary members one fellow in each district.

It shall concern itself with the relations between the fellows of the Society and hospitals.

Dr. Blaisdell called the Council's attention to the fact that this was a new section both in language and principle. He pointed out that there were more than 5500 members of the Massachusetts Medical Society, most of whom had very definite relationships with hospitals, and that there was now no machinery in the Society endowed with authority to confer on matters pertaining to these relationships. He emphasized that this was not a witch-hunting committee. He added that the program of medical-care costs insurance upon which we are about to embark was bound to bring up problems which could be handled amiably by such a committee. He pointed out that many physicians will during the next two years be forced to give up staff positions as they enter the armed forces of our Country. He added, "What is to become of these men when they return to civilian practice? Here again is a fruitful field in which such a committee might serve a very useful purpose."

Dr. Blaisdell moved the adoption of this section. This motion was seconded by Dr. Jankelson.

Dr. Donald Munro, Suffolk, registered his opposition to the adoption of this section. He said that such a committee sooner or later would be called upon to decide whether Dr. A in Community B is to be admitted to a closed hospital staff. He added in substance that he was sure that it would be wrong for the Massachusetts Medical Society to authorize any action which would allow for the destruction of the worth-while objectives which had been built up in the care of the sick by the closed hospital staff.

Dr. Cheever thought the relationship herein involved might very well be handled by the Committee on Public Relations.

Dr. Blaisdell agreed that the Committee on Public Relations might handle this problem. He believed, however, that it would be done better by a standing committee. He believed that this proposed committee was no more likely to get into trouble than was any other committee.

Dr. Hornor said that this was the specific article in the text as offered to which he objected. He, too, thought that the business here concerned might very well be handled by the Committee on Public Relations.

Dr. Carl Bearse said that the Medical Society of the State of New York had such a committee as

is herein proposed. He quoted the secretary of this society as saying that he thought offhand that it is the most natural thing in the world that medical societies should create committees of this kind.

Dr. Elmer S. Bagnall, Essex North, expressed himself as favoring a Committee on Hospital Relations. He spoke of the former practice of the Committee on Public Relations whereby there was created, within the committee, subcommittees which considered specific problems having to do with public relations. He said that this method of organizing the committee's work had been given up in favor of the appointment of special committees by the Council which would, on a public-relations matter, report its findings to the Council through the Committee on Public Relations.

Dr. Robert N. Nye, Suffolk, asked what had been the stand of the Executive Committee as to this section when it conducted its review of these proposed by-laws.

Dr. Blaisdell answered that the Committee was in opposition.

Dr. Nathaniel W. Faxon, Suffolk, said that he favored the creation of such a committee provided it would function along the lines as suggested by Dr. Blaisdell. He believed that the Committee on Public Relations might successfully continue to function in hospital problems. He added, however, that a committee which concerned itself very definitely with hospital problems might function better.

Dr. Felton thought that this section was loaded with political dynamite.

Dr. Lewis S. Pilcher, Middlesex South, could not understand how the creation of this committee would affect the status of hospitals with closed staffs.

Dr. Bagnall pointed out that a committee of this sort would report to the Council and not embark on any wild venture on its own initiative.

Dr. William E. Browne, Suffolk, asked Dr. Blaisdell as to whether or not the committee was to have certain definite and outlined duties.

Dr. Blaisdell answered, "No; the duties would be broad." He said this committee might even deal with the question of whether the "steak shall be rare or well done." He did not, however, anticipate it would do any such thing. He believed that such a committee would be governed by at least a modicum of common sense.

Dr. Fallon expressed the opinion that the creation of this committee might very well turn out to be one of the most important things the Society has ever done. He added that he believed that we could trust the President to appoint fellows to this committee who would use their powers reasonably.

Dr William B Breed, Suffolk, was fearful of delegating to such a committee broad and far-reaching powers. He thought that the activities of this committee should be limited.

Dr Phippen recalled that during his term as President, he had appointed a committee of this general character. He asked why this committee could not take on the duties of the proposed new committee. The Secretary confirmed the existence of the committee referred to by Dr Phippen and said it was known as the Committee Appointed to Confer with the Massachusetts Hospital Association. He added that this committee had not been very active.

Dr Lund had the same view as did Dr Breed. Dr David L. Halbersleben, Norfolk, spoke in favor of the section and complimented the Committee on By Laws for its foresight.

Dr William J. Walton, Norfolk, also spoke in favor of the section.

Dr Ober called for a vote by ballot. Dr Blaisdell moved that the Council recess until 7:00 p.m. This motion was seconded and on a vote the Council recessed at 12:00 p.m.

The Council reconvened at 2:00 p.m. Dr Ober called for the result of the ballot.

The Secretary announced that 79 fellows voted for the retention of this section and 84 against.

Dr Ober announced that Section 15 of Chapter VII of the text had not been adopted.

Dr Michichin moved that the matter of hospital relations be referred to the Committee on Public Relations. The motion was seconded by Dr Beare and adopted by vote of the Council.

Dr Edward P. Bagg, vice president of the Massachusetts Medical Society, assumed the chair.

Dr Ober moved that Chapter VII of the text be amended by adding the following as Section 15.

*Section 15.* The Committee on Industrial Health shall consist of seven fellows.

It shall concern itself with medical and surgical problems in industry.

It shall consult with an advisory committee made up of representatives of agencies and others concerned with industrial health, appointed by the President.

The motion was seconded by Dr Henderson and it was so ordered by vote of the Council.

Dr Ober resumed the chair.

Dr Blaisdell presented Chapter I, Section 1, the text of which reads as follows:

#### CHAPTER I FELLOWSHIP

*Section 1.* Applicants for fellowship in the Massachusetts Medical Society are required to satisfy the censors that they are not less than twenty-one years of age, that they are of sound mind and of good character, that they have a Baccalaureate or Doctorate of Medicine from a medical school approved by the

Council or have received the approval of the Committee on Membership, that they have received a license to practice medicine within the United States, or its territories, that they do not practice medicine in a manner contrary to the code of ethics of the Society, that they have made application according to the provisions of Chapter V, and that they have paid the examination fee of three dollars.

They shall appear personally before the censors and satisfy them that the above requirements are fulfilled.

Dr Blaisdell moved the adoption of this section. The motion was seconded by Dr Munro.

Dr Frothingham inquired whether or not a professor in a medical school, who was not licensed, would be eligible for membership under this section. Dr Ober answered by saying that there is another by-law which will deal with this matter.

This section was adopted by vote of the Council.

Dr Blaisdell moved the deletion of Section 1 of Chapter I of the by-laws as amended in 1941. This motion was seconded by Dr Smith and it was so ordered by vote of the Council.

Dr Blaisdell presented Chapter I, Section 2, of the text which reads as follows:

*Section 2.* Applicants found to be so qualified shall on paying the assessment for the current fiscal year (except as hereafter provided in Section 6 of this chapter) and subscribing to the by-laws and code of ethics all within two weeks from the date of their examinations, be approved by the censors.

They furthermore shall on confirmation by the president and by the secretary of the Society, be admitted fellows of the Society and shall receive certificates of fellowship in testimony thereof signed by the President and by the Secretary.

Dr Blaisdell moved its adoption. The motion was seconded by Dr William M. Collins, Middlesex North, and it was so ordered by vote of the Council.

Dr Blaisdell moved the deletion of Section 2 of Chapter I of the by-laws as amended in 1941. The motion was seconded by Dr Curley and it was so ordered by vote of the Council.

Dr Blaisdell presented Section 3 of Chapter I of the text which reads as follows:

*Section 3.* Fellows having a legal residence in Massachusetts shall be known as resident fellows; all others as nonresident fellows.

Nonresident fellows shall receive the official publications of the Society and may attend Society meetings but may not vote, hold office or receive protection under the medical defense act of the Society.

Dr Blaisdell moved the adoption of this section. The motion was seconded by Dr Bagg and it was so ordered by vote of the Council.

Dr Blaisdell moved the deletion of Section 3 of Chapter I of the by-laws as amended in 1941. Dr Chereskin seconded the motion and it was so ordered by vote of the Council.

Dr. Blaisdell presented Chapter I, Section 4, which reads as follows:

*Section 4.* 'Honorary fellowship may be conferred on distinguished members of the medical profession.

Associate fellowship may be conferred on eminent workers in the allied sciences.

Such fellowships may be conferred by a two-thirds vote of the Council at a stated meeting, provided written nominations therefor have been submitted by two or more fellows at a previous stated meeting and have been approved by the Committee on Membership.

Honorary and associate fellows may attend and address meetings of the Society, but shall not be accorded other rights or privileges, or be subject to assessment.

Dr. Blaisdell moved the adoption of this section. Dr. Fallon seconded the motion and it was so ordered by vote of the Council.

Dr. Blaisdell moved that Section 4, Chapter I, of the by-laws as amended in 1941 be deleted. The motion was seconded by Dr. Fallon and it was so ordered by vote of the Council.

Dr. Blaisdell presented Section 5 of Chapter I, which reads as follows:

*Section 5.* Fellows who are sixty-five years of age or older whose assessments have been paid or remitted may, by vote of the Executive Committee, acting on recommendation of the Committee on Membership, become retired fellows.

They shall be in good standing, and may attend and address meetings of the Society, but shall not be accorded other rights or privileges, except that, on request annually, they shall receive the publications of the Society.

They shall not be subject to assessment.

Applications for retirement shall be addressed to the Executive Committee and sent to the Treasurer.

Retired fellows may, on their own request, be restored to active fellowship by the Executive Committee.

Dr. Blaisdell moved the adoption of this section calling the attention of the Council to the effect that the last three lines had previously been deleted by unanimous consent. The motion was seconded by Dr. Fallon.

Dr. Cheever thought it too bad that the retired members should be required to ask annually that the *Journal* be sent to them. Dr. Bearse explained that retired members frequently change their residence without notifying the Secretary of the change. The *Journal* continues to go to the old address and nobody receives it. Dr. Cheever expressed his content at this explanation.

The motion was adopted by vote of the Council.

Dr. Blaisdell moved the deletion of Section 5 of Chapter I of the by-laws as amended in 1941. The motion was seconded by Dr. Fallon and it was so ordered by vote of the Council.

Dr. Blaisdell presented Section 6 of Chapter I which reads as follows:

*Section 6.* Fellows shall be assessed such sums as are voted by the Council, and such additional sums as are voted by the district societies for their own use.

The fiscal year shall begin on the first day of January. Assessments shall be paid in advance. The first assessment paid by a fellow admitted to the Society following the December examinations shall cover his dues for the succeeding fiscal year and shall be the amount fixed for that year.

Assessments may be remitted by the Executive Committee on recommendation by the Committee on Membership.

Whenever a fellow owing more than one annual assessment pays in part, the payment or payments so made shall be considered as on the assessment or assessments longest due and for no others.

Dr. Blaisdell announced that Dr. Harold R. Kurth, Essex North, would lead the discussion on this section.

Dr. Kurth explained that by this section it was proposed to make the payment of district society assessments one of the conditions of membership in the Massachusetts Medical Society. He added that under the old by-laws, district societies had no law under which they could compel individual members to meet assessments voted by them and that this section would correct this situation.

Dr. Blaisdell moved the adoption of the section. The motion was seconded by Dr. Fallon and it was so ordered by vote of the Council.

Dr. Blaisdell moved the deletion of Section 6 of Chapter I of the by-laws as amended in 1941. The motion was seconded and it was so ordered by vote of the Council.

Dr. Blaisdell presented Section 7 of Chapter I which reads as follows:

*Section 7.* Resignations shall be submitted in writing to the Treasurer, who shall deliver them to the Committee on Membership.

This committee shall submit them with recommendations to the Executive Committee for action.

Resignations shall be accepted only from fellows whose assessments have been remitted or paid in full.

Dr. Blaisdell moved the adoption of this section. The motion was seconded by Dr. Fallon and it was so ordered by vote of the Council.

Dr. Blaisdell moved the deletion of Section 7 of Chapter I of the by-laws as amended in 1941. Dr. Fallon seconded the motion and it was so ordered by vote of the Council.

Dr. Blaisdell presented Section 8 of Chapter I which reads as follows:

*Section 8.* Fellows who, despite notification by registered letter from the Treasurer, have not paid assessments for two years, or who, despite notification by registered letter from a district treasurer, have not paid the assessments of their district society for two years, shall be deprived of the privileges of fellowship by the Executive Committee, acting on a report of the Committee on Membership, unless otherwise ordered.

Dr Blaisdell moved the adoption of this section. The motion was seconded by Dr Fallon.

Dr Browne asked if it would not be well to insert after the words "registered letter" the words "personal receipt be requested." Dr Blaisdell agreed that these words could be put in but the cost would be increased.

Dr Bignall inquired if it was clear what the words "unless otherwise ordered," meant. Dr Blaisdell said that by the use of these words, reference is made to the machinery by means of which dues are remitted.

Dr Chereskin asked how this would affect men who had gone to war. Dr Blaisdell answered that this contingency had been cared for by the Council a year ago.

Dr Blaisdell's motion to adopt this section was carried by vote of the Council.

He moved to delete Section 8 of Chapter I of the by laws as amended in 1941. Dr Fallon seconded the motion and it was so ordered by vote of the Council.

Dr Blaisdell presented Section 9 of Chapter I which reads as follows:

*Section 9* Fellows who have been convicted in a court of law of a crime involving moral turpitude or who have been guilty of attempts to harm the Society or to injure its usefulness of advertising nostrums for sale or otherwise offering them to the public or professing to cure disease by secret methods of gross violations of these by laws, of the code of ethics of the Society or of the American Medical Association of presenting false certificates or false statements of character or of educational requirements, of accepting rebates on prescriptions or appliances, or of any other conduct unbecoming a physician, may be expelled from the Society or otherwise disciplined as provided in Chapter VIII, Section 9.

A fellow who has been deprived of his license to practice medicine in the Commonwealth shall automatically cease to be a fellow of the Society.

Dr Munro called attention to the fact that earlier in the meeting the Council had given unanimous consent to change line 15 of this section so as to read Chapter VII, Section 9, and Chapter VIII, Section 1. Dr Blaisdell moved the adoption of Section 9 of Chapter I. The motion was seconded by Dr Fallon.

Dr James P. O'Hare, Suffolk, asked what was meant by the words "to injure its usefulness." Dr Fallon thought these words might be stricken out. Dr Ober asked Dr Fallon and Dr Rice to collaborate on an amendment looking toward this end.

Dr Blaisdell, in the meantime, presented Chapter I, Section 10, which reads as follows:

*Section 10* Former fellows who desire to be readmitted following retirement resignation not requested by the Committee on Ethics and Discipline, or deprivation of fellowship for arrears shall make appli-

cation in writing addressed to the Executive Committee and sent to the Secretary.

Such applications shall be referred for investigation to the board of membership of the district society concerned, which shall report with recommendations to the Committee on Membership.

This committee shall report with recommendations to the Executive Committee.

The Executive Committee may readmit former fellows so recommended.

Dr Blaisdell moved the adoption of Section 10 of Chapter I. The motion was seconded by Dr Bearse and adopted by vote of the Council.

Dr Blaisdell moved the deletion of Section 10 of Chapter I of the by laws as amended in 1941. This motion was seconded by Dr Bearse and it was so ordered by vote of the Council.

Dr Frothingham said that he still did not see how a man who was not licensed to practice medicine could become a member of the Massachusetts Medical Society.

Dr Blaisdell answered that a man who was an M.D. but without a license to practice could become an honorary member. He added that it is the feeling that the Society should be made up of fellows who are practicing medicine.

Dr Blaisdell presented Chapter II in its entirety. This chapter reads as follows:

## CHAPTER II

### MEETINGS OF THE SOCIETY

*Section 1* The annual meeting of the Society shall be held in Boston on the second Wednesday of June, unless otherwise ordered by the Council.

The order of business shall be: (1) reading of the record of the last annual meeting; (2) report by the Secretary of changes in membership during the year; (3) report by the President on the state of the Society; (4) such other business as may lawfully come before the meeting; (5) annual oration.

*Section 2* Special meetings of the Society may be called by the President or by vote of the Council, and shall be called on written request by ten councilors or one hundred fellows.

*Section 3* The deliberations of the Society shall be governed by parliamentary usage as interpreted by *Roberts' Rules of Order*, when not in conflict with the by laws of the Society.

One hundred fellows shall constitute a quorum.

Dr Blaisdell moved the adoption of Chapter II. The motion was seconded by Dr Bearse and it was so ordered by vote of the Council.

Dr Blaisdell moved the deletion of Chapter II of the by laws as amended in 1941. The motion was seconded by Dr Bigg and it was so ordered by vote of the Council.

Dr Blaisdell presented Sections 1, 2, 3 and 4 of Chapter III which he said might very well be considered together. These sections read as follows:



## CHAPTER III

## DISTRICT SOCIETIES

*Section 1.* The boundaries of district societies may be changed, and new districts may be established, by the Council.

*Section 2.* The membership of each district society shall consist only of such fellows, whether active or retired, as have legal residences within the boundaries of the district, except in cases decided otherwise by vote of the Executive Committee.

*Section 3.* Any fellow wishing to transfer membership from one district society to another without a change of legal residence must so petition the Committee on Membership in writing, stating his reasons therefor.

The Committee on Membership shall report, after consultation with the officers of the two districts concerned, its recommendations to the Executive Committee for action.

*Section 4.* Each district society may adopt by-laws and regulations for the government of its own affairs and levy assessments, provided such by-laws and regulations are not in conflict with those of the Society.

Dr. Blaisdell moved the adoption of these sections of Chapter III. The motion was seconded by Dr. Kurth and it was so ordered by vote of the Council.

Dr. Blaisdell moved the deletion of Sections 1, 2, 3 and 4 of Chapter III of the by-laws as amended in 1941. The motion was seconded by Dr. Fallon and it was so ordered by vote of the Council.

Dr. Fallon, at this point, presented an amended Section 9 of Chapter I which reads as follows:

*Section 9.* Fellows who have been convicted in a court of law of a felony involving moral turpitude, or of a crime, or who have been guilty of attempts to harm the Society; of advertising nostrums for sale or otherwise offering them to the public, or professing to cure disease by secret methods; of gross violations of these by-laws, of the code of ethics of the Society or of the American Medical Association; of presenting false certificates or false statements of character or of educational requirements; of accepting rebates on prescriptions or appliances; or of any other conduct unbecoming a physician, may be expelled from the Society or otherwise disciplined as provided in Chapter VII, Section 9 and Chapter VIII, Section 1.

A fellow who has been deprived of his license to practice medicine in the Commonwealth shall automatically cease to be a fellow of the Society.

Dr. Fallon moved the adoption of the amendment to Section 9 of Chapter I. Dr. Collins seconded the motion and it was so ordered by vote of the Council.

Dr. Blaisdell moved the adoption of Section 9 of Chapter I as amended. Dr. Fallon seconded the motion, and it was so ordered by vote of the Council.

Dr. Blaisdell moved the deletion of Section 9 of Chapter I of the by-laws as amended in 1941. The

motion was seconded by Dr. Fallon and it was so ordered by vote of the Council.

Dr. Blaisdell presented Section 5, of Chapter III which reads as follows:

*Section 5.* Each district society shall hold its annual meeting between the fifteenth day of April and the fifteenth day of May.

Each district society at this meeting shall elect by ballot from its active fellows: a president, who shall be *ex officio*, a vice-president of the Society; a vice-president; a secretary; a treasurer; councilors as below specified; four censors; a supervising censor; a commissioner of trial; a member of the Committee on Public Relations; a member of the Committee on Legislation; a member and alternate member of the Committee on Nominations.

Councilors shall be elected in number equal to one for every twenty active and retired fellows and a majority fraction thereof, as of the first day of January preceding.

Only councilors shall be eligible as supervising censors and members of the Committee on Public Relations and the Committee on Legislation.

Only councilors who have held this office for at least one year shall be eligible as members of and alternates to the Committee on Nominations. Members of and alternates to the Committee on Nominations shall not serve for more than five consecutive years and shall not be eligible for re-election for three years thereafter.

Only fellows who have been members of the Society for at least ten years shall be eligible as censors or supervising censors. The term of the supervising censors shall be five years. They shall not immediately succeed themselves. All supervising censors shall have been censors previously.

Councilors, censors, supervising censors, members of the Committee on Public Relations, members of the Committee on Legislation, members of the Committee on Nominations, and commissioners of trial shall take office at the close of the next annual meeting of the Society.

The councilors of each district society shall meet on call by the secretary at or as soon as possible after the annual meeting of the district society and elect two of their number to serve as member and alternate of the Executive Committee, in accordance with Chapter VII, Section 2.

Members of and alternates to the Executive Committee shall serve for three years and shall not be eligible for re-election for three years thereafter.

The terms of office of the alternate shall be concurrent with the term for which the member was elected.

Vacancies that occur during the term of office of such member or alternate shall be filled promptly, by vote of the councilors of the district concerned, *ad interim*.

Dr. Kurth led the discussion on this section. He called the Council's attention to the fact that this section contained many changes. He said that the committee recognized that members of the Nominating Committee should have some experience in the work of the Council. He added that the committee felt that a fellow could be a member of the Nominating Committee too long. Hence the restriction on the number of consecutive years that

any councilor could serve. He pointed to the change as it concerned the term of office of a supervising censor and added that it was important that a supervising censor retain this office over a period of years so as to become thoroughly conversant with this highly important work. He said that the final change of importance provided that the officers of the Society take office at the close of the next annual meeting of the Society instead of the day preceding this meeting.

Dr Kurth moved the adoption of Section 5 of Chapter III. Dr Beirse seconded the motion.

Dr George C. Tully, Worcester, called the Council's attention to an inconsistency which appears in line 2 of Section 4 of the text when compared with the present section under consideration. He said that, in line 2 of Section 4, the word "councilor" should be substituted for the word "fellow." Dr Blaisdell indicated that the point was well taken.

Dr Munro believed that the words "shall not immediately succeed themselves," should be deleted, since, otherwise, all the supervisors elected this year would go out of office at the same time. He moved that lines 30 and 31, beginning with the word, "They," and ending with the word "themselves," be deleted. Dr Fallon seconded this motion, which was adopted by vote of the Council.

Dr Macchichlan moved that lines 33 to 38 of Section 5 be deleted. Dr Rice seconded the motion, and it was so ordered by vote of the Council.

Dr Kurth moved the adoption of Section 5 of Chapter III as amended. Dr Fallon seconded the motion. There were several questions from councilors anent this section, all of which had for their purpose the clarification of thought with regard to it. The motion was adopted by vote of the Council.

Dr Blaisdell moved the deletion of Sections 5 and 6 of Chapter III of the by laws as amended in 1941. Dr Fallon seconded the motion, and it was adopted by vote of the Council.

Dr Blaisdell presented Section 6 of Chapter III, which reads as follows:

*Section 6.* The secretary of each district society promptly after its annual meeting shall report on appropriate forms, to the Secretary the names and residences of fellows elected, as provided in Chapter III, Section 5.

He shall promptly notify the Secretary, on the required form, of deaths of fellows in his district.

He shall also perform such duties as are defined in Chapter V.

He shall call, at or as soon as possible after the annual meeting of the district society, and before the annual meeting of the Society, meetings of the district councilors to elect the member and alternate of the Executive Committee, and shall send to the Secretary the names of the member and alternate chosen.

He shall see that a new member or alternate is chosen in a similar manner to fill a vacancy as it occurs, as provided in Section 5.

Dr Macchichlan and Dr Fallon were directed by Dr Ober to retire and confer on this section.

Dr Blaisdell presented Section 7 of Chapter III, which reads as follows:

*Section 7.* The treasurer of each district society shall collect the assessments of his district.

He shall furnish a list of fellows two years in arrears to the Committee on Membership for action as provided in Chapter I, Section 8.

Dr Kurth, in leading the discussion, said that, under the by laws as amended in 1941, the district treasurer receives fifty cents for any dues that he collects and that the money goes to him personally. He added that the committee believes that, in this day when finances are important and when there will be a loss of revenue to the Society because of the remission of the dues of those entering the Service, it would be better that this money, which amounts to about \$750, go into the treasury of the Society. He added that unquestionably part of the \$750 would be returned in dividends to the district societies. Dr Kurth moved the adoption of Section 7 of Chapter III. Dr Jankelson seconded the motion.

Dr George L. Steele, Hampden, thought that, if it was the intent not to pay the district treasurer the 5 per cent, it should be so stated in the motion.

Dr Alexander A. Levi, Middlesex South, asked that action on this section be postponed until after the discussion on Chapter V, Section 3, giving as his reason a desire to offer an amendment which might affect the section under discussion. The question was demanded from several sources. The motion was put by the President and adopted by vote of the Council.

Dr Blaisdell moved the deletion of Section 8 of Chapter III of the by laws as amended in 1941. The motion was seconded by Dr Washburn and adopted by vote of the Council.

Dr Blaisdell presented Sections 1 and 2 of Chapter IV which read as follows:

## CHAPTER IV

### THE COUNCIL

*Section 1.* The Council shall consist of councilors chosen by the district societies, the president, ex president, president elect, vice president, vice presidents *ex officio*, secretary, treasurer, and assistant treasurer of the Society, the secretaries of the district societies and the chairmen of all standing committees.

The Council each year shall hold three stated meetings in Boston unless otherwise ordered by the Council. The annual meeting shall be held on the day next preceding the annual meeting of the Society. A stated meeting shall be held on the first Wednesday in October, and another, on the first Wednesday in February.

Special meetings may be called by the President, by vote of the Council, or by the written request of ten councilors.

*Section 2.* The deliberations of the Council shall be governed by parliamentary usage as contained in *Roberts' Rules of Order*, when not in conflict with the by-laws of the Society.

Fifty councilors shall constitute a quorum.

Dr. Blaisdell moved the adoption of Sections 1 and 2 of Chapter IV. Dr. Fallon seconded the motion.

Dr. Day thought that the district secretaries and the district treasurer, both, should be *ex-officio* members of the Council.

The motion was adopted by vote of the Council.

Dr. Blaisdell moved the deletion of Sections 1 and 2 of Chapter IV of the by-laws as amended in 1941. Dr. Fallon seconded the motion, and it was so ordered by vote of the Council.

Dr. Fallon now made reference to Chapter III, Section 6, on which he and Dr. MacLachlan had previously been directed to confer.

Dr. Fallon offered the following amendments to Section 6 of Chapter III: in line 13 the word "councilors" shall read "councilors-elect." The reference in line 19, should be "as provided in Chapter III, Section 5." Dr. Bearse seconded the first of these amendments and Dr. O'Hare the second. These were both adopted on vote by the Council.

Dr. Blaisdell moved the adoption of Section 6 of Chapter III as amended. This motion was seconded by Dr. Fallon, and it was so ordered by vote of the Council.

Dr. Blaisdell moved the deletion of Section 7 of Chapter III of the by-laws as amended in 1941. Dr. Fallon seconded the motion, and it was so ordered by vote of the Council.

Dr. Blaisdell presented Section 3 of Chapter IV of the text, which reads as follows:

*Section 3.* The Council at its annual meeting, on nomination by the Committee on Nominations or from the floor, shall elect by ballot officers of the Society as follows: president-elect, who shall serve as president-elect until the second annual meeting of the Society after his election and shall, unless otherwise voted by the Council, become president on his installation in the course of that meeting, serving thereafter as president until the installation of his successor; a vice-president, secretary, treasurer, and assistant treasurer, all of whom shall assume the duties of office at the close of the annual meeting of the Society and shall hold office until their successors have been duly elected. Councilors only shall be eligible to the offices above-named.

The Council, in event of the death or the incapacity of the President-Elect, shall elect a president by ballot, at its next annual meeting, on nomination by the Committee on Nominations or from the floor.

The Council, at its annual meeting, on nomination by the Committee on Nominations or from the floor,

shall elect by ballot a fellow to deliver an oration at the annual meeting of the Society the following year.

The Council at its annual meeting shall elect, on nomination by the President-Elect or from the floor, standing committees to serve for one year from the close of the annual meeting as follows: on Arrangements; on Publications; on Membership; on Ethics and Discipline; on Medical Education; on Public Health; on Medical Defense; on Society Headquarters; on Finance; and on Hospital Relations.

Dr. Blaisdell pointed out that this section included several new ideas: namely, that the President-Elect shall take office at the second annual meeting of the Society after his election (this is to correct a bad situation in the by-laws as amended in 1941); that a provision is made for an assistant treasurer, which will be considered under a separate article; that the words "unless otherwise ordered by the Council" protect the Society in the event that the President-Elect is found unworthy to succeed as president; that, in the case of the death or the incapacity of the President-Elect, a provision was made for the continuity of the office of president; and that the President-Elect shall nominate committees which will serve during his term of office.

Dr. Bearse moved as an amendment that the words "Hospital Relations" in lines 33 and 34 be deleted and the words "Industrial Health" be substituted. The amendment was seconded by Dr. Smith, and it was so ordered by vote of the Council.

Dr. Blaisdell moved the adoption of Section 3 of Chapter IV as amended. This motion was seconded by Dr. Fallon.

Dr. Nye raised the point that this section should either make reference to Chapter VI, Section 1, as this latter concerns the nomination of committees by the President in case of the death of the President-Elect, or that the section under discussion should itself provide for this contingency.

Dr. Nye, Dr. Fallon and Dr. Bearse were directed by Dr. Ober to confer on this section. They did so and Dr. Fallon offered the following amendment to Section 3 of Chapter IV: insert after the word "floor" the phrase "or as provided in Chapter VI, Section 1." Dr. Munro seconded the amendment, and it was so ordered by vote of the Council.

Dr. Blaisdell's motion for the adoption of Section 3 of Chapter IV as amended was seconded by Dr. Fallon, and it was so ordered by vote of the Council.

Dr. Blaisdell moved the deletion of Section 3 of Chapter IV of the by-laws as amended in 1941. The motion was seconded by Dr. Fallon, and it was so ordered by vote of the Council.

Dr. Blaisdell presented Sections 4, 5, 6 and 7 of Chapter IV, which read as follows:

*Section 4* The Council shall elect at the stated meeting in October, on nomination by the President or from the floor, the Auditing Committee, composed of two fellows who are not councilors

This committee, following the close of the fiscal year, shall require by a certified public accountant an examination of the assets and securities of the Society in the custody of the Treasurer, and of the Treasurer's books and accounts

This committee shall verify the accountant's examination and report its findings at the stated meeting of the Council in February

*Section 5* The Council may at any meeting fill vacancies in office or elect committees

*Section 6* The Council may vote to establish or abolish sections for the consideration of scientific papers at the annual meetings of the Society, and shall appoint the first chairman and secretary of a new section so established

Each section shall elect annually a chairman and a secretary to serve for one year from the close of the annual meeting at which they are elected

The duties of these officers shall be to arrange the programs of the meetings of their sections under the rules of the Council

The chairman shall preside at the meetings of the section at the following annual meeting, the secretary shall take charge of the papers presented and shall transmit them promptly to the editor of the official journal of the Society

*Section 7* The Council shall, on nomination by the President or from the floor, elect delegates to the House of Delegates of the American Medical Association in accordance with the by laws of that association

It may, on nomination by the President or from the floor, elect delegates to such other medical meetings as it deems suitable

Dr Blaisdell moved the adoption of Sections 4, 5, 6 and 7 of Chapter IV. The motion was seconded by Dr Kurth, and it was so ordered by vote of the Council

Dr Blaisdell moved the deletion of Sections 4, 5, 6 and 7 of Chapter IV of the by laws as amended in 1941. The motion was seconded by Dr Brain and F Conley, Middlesex South, and it was so ordered by vote of the Council

Dr Blaisdell presented Section 8 of Chapter IV, which reads as follows

*Section 8* The Council shall vote the salaries of its officers and employees, the appropriations for its officers and committees, and such other appropriations as it deems suitable

No officer or committee shall exceed the voted appropriation

No salary to any officer or employee and no regular appropriation shall be increased except on recommendation of the Committee on Finance and by vote of the Council

The Treasurer is authorized, on recommendation of the Committee on Finance to pay such monies as may be necessary in the event of emergency, the expense of which shall be determined by the President

Dr Blaisdell moved the adoption of Section 8 of Chapter IV. The motion was seconded by Dr

Conley. It was so ordered by vote of the Council

Dr Blaisdell moved the deletion of Sections 8 and 9 of Chapter IV of the by laws as amended in 1941. The motion was seconded by Dr Fallon and it was so ordered by vote of the Council

Dr Blaisdell presented Section 1 of Chapter V which reads as follows

## CHAPTER V

### CENSORS AND SUPERVISING CENSORS

*Section 1* The supervising censors shall constitute a Board which shall meet annually on the day appointed for the annual meeting of the Council. This board shall elect a chairman and also three of their members to sit with the Committee on Membership. Five supervising censors shall constitute a quorum

The secretary of the Society shall act as secretary of the Board. He shall call special meetings at the request of the chairman or five supervising censors. He shall keep a permanent record of the proceedings of the Board and shall provide materials necessary for conducting examinations of applicants for fellowship

The Board at its annual meeting shall adopt a uniform plan for the examination of applicants

The supervising censors, on request, shall be paid traveling expenses

The supervising censors shall be chairmen of their respective boards of censors and shall cause the examinations of applicants to be conducted in strict conformity to the plan adopted by the Board of Supervising Censors

The censors of the several district societies shall meet for the examination of applicants semiannually on the first Thursday in May and on the first Thursday in December

The approval of at least three censors shall be necessary to qualify an applicant

An applicant failing two examinations may not again apply until three years have elapsed from the date of the last application

Dr Fallon led the discussion on this section and moved its adoption. The motion was seconded by Dr Munro, and it was so ordered by vote of the Council

Dr Fallon moved the deletion of Section 1 of Chapter V of the by laws as amended in 1941. The motion was seconded by Dr Bearse and it was so ordered by vote of the Council

Dr Fallon presented Section 2 (a) of Chapter V which reads as follows

*Section 2 (a)* The secretary of a district society may receive not later than February 15 for the censors' examination in May or later than September 15 for the examination in December an application for fellowship submitted on the proper form by an applicant whose legal residence is within the district of that society

The secretary of the Suffolk District Society may receive and officials of that society may act on an application for nonresident fellowship

The secretary of the district society shall verify each applicant's diploma and deliver his application to the Secretary not later than February 20 or September 20, respectively

The official journal shall publish, in the first number on or after March 5 or October 5, a list of all applicants. This list shall include name, address, medical school and date of graduation of the applicant; name and address of the secretary of the district society concerned; and if a sponsor is required, the name and address of the sponsor.

Fellows are requested to send to the secretary of the district society concerned, *not later than*, respectively, March 20 or October 20, *confidential* written opinions on the qualifications of applicants.

Dr. Fallon announced that there was a misprint in the third line—the word “or” should be changed to “nor.” He moved the adoption of Section 2 (a) of Chapter V. The motion was seconded by Dr. Bearse, and it was so ordered by vote of the Council.

Dr. Fallon moved the deletion of Section 2 (a) of Chapter V of the by-laws as amended in 1941. The motion was seconded by Dr. Bearse, and it was so ordered by vote of the Council.

Dr. Fallon presented Section 2 (b) of Chapter V, which reads as follows:

(b) The secretary of a district society shall receive an application from a graduate of a discontinued medical school, a foreign medical school or any medical school not approved by the Council only when:

The applicant has possessed a license to practice medicine in the United States or its territories for at least five years;

The applicant has submitted with his application the name and address of a sponsor who is a fellow of the district society concerned; and

The sponsor has caused to be delivered by fellows of the Society to the secretary of the district society *confidential* written opinions on the qualifications of the applicant.

He pointed out that the committee felt that an applicant for membership in the Massachusetts Medical Society should have practiced for five years in the United States before being eligible for membership. He said that there were some members who felt that such an applicant should have practiced for five years in Massachusetts before being so eligible. The committee did not share this latter view because it felt that our means of intercommunication was such that we could obtain sufficient information about a prospective candidate no matter in what state or states he had practiced.

Dr. Fallon moved the adoption of Section 2 (b) of Chapter V. This motion was seconded by Dr. Bearse.

Dr. Alexander A. Levi, Middlesex South, moved as an amendment that in line 32 after the word “years” the following be inserted: “This license shall be verified by the district secretary and the data relating to it shall be recorded in the applicant’s application blank.” Dr. Bearse seconded

the amendment, and it was so ordered by vote of the Council.

Dr. Munro said that, in connection with the five-year law, he had taken the liberty of writing to the supervising censors and that 85 per cent of them believed that residence in Massachusetts for five years should be one of the requirements of eligibility. He, therefore, moved that the phrase in line 31 of Section 2 (b) of Chapter V, reading “in the United States or its territories” be deleted and that the phrase “in the Commonwealth of Massachusetts” be substituted. The motion was seconded by Dr. Hornor.

Dr. Robert T. Monroe, Norfolk, in opposing the amendment spoke as follows:

The Committee on Medical Education has objected strenuously and seriously on every occasion to the five-year rule directed against the graduates of foreign medical schools, always on the ground that injustice is done in particular instances if this rule is applied to all. When this job was taken out of its hands and put in the hands of the Committee on Membership, at our last meeting there seemed to be some feeling that the Society is being flooded with fellows from foreign medical schools. That has not been shown in the one year that I have been on the committee, and I can give figures from the last examination on April 4 of this year. Twenty-three graduates of foreign medical schools were considered by the committee, and of these 12 were rejected and 11 were accepted; of the 11 accepted, 6 were born in the United States and took their medical work abroad, 2 are not citizens, 1 has been in this country for a little over five years and has a good job and 2 are professors of medicine rather lately come to this country—one who came to take a professorship in Harvard last fall and the other, an Australian, who has a professorship at Tufts Medical School. From those figures there is no evidence that we are being flooded by graduates of foreign medical schools in this Society.

I object not only strenuously to leaving in the term “in the United States or its territories,” but I object still more strenuously to limiting it to Massachusetts.

Dr. Munro’s amendment was put to a vote by the President and lost, the vote being 26 for and 34 against.

Dr. Monroe moved to amend Section 2 (b) of Chapter V by striking out the words “in the United States and its territories.” This motion was seconded by Dr. Lund.

Dr. Fallon believed that the text should, in respect to Section 2 (b) of Chapter V, remain as it is. He pointed out that we should not only be concerned with an applicant’s scientific attainments but that there should likewise be available to us some knowledge as to how he comports himself. He added that such knowledge can only be had when the applicant resides amongst us for a reasonable time or when there is readily available to us information on this point from those among

whom the applicant has resided for such reasonable time.

Dr. Curley favored the retention of the text as it stands.

Dr. Lund advocated the adoption of Dr. Munroe's amendment.

Dr. Munro said that he felt that the reasons advanced against this five-year restriction were not valid.

There was a demand for the question from several sources.

Dr. Ober put the question, and the amendment was lost. Dr. Fallon withdrew his original motion, and Dr. Bearse withdrew his second.

Dr. Fallon moved the adoption of Section 2 (b) as amended. The motion was seconded by Dr. Bearse, and it was so ordered by vote of the Council.

Dr. Fallon moved the deletion of Section 2 (b) of Chapter V of the by-laws as amended in 1941. The motion was seconded by Dr. Bearse and it was so ordered by vote of the Council.

Dr. Fallon presented Section 2 (c) of Chapter V which reads as follows:

(c) The censors may admit to examination an applicant who is a graduate of a discontinued, foreign or unapproved medical school only when such applicant has been considered by the board of membership concerned and approved by the Committee on Membership.

The board of membership of a district society shall consist of the president, secretary and supervising censor.

It shall gather such information as it deems advisable to determine whether an applicant is conscientious, capable and reputable. It shall interview personally such applicant. It shall either approve or disapprove him for examination by the censors.

The secretary of the district society shall deliver to the chairman of the Committee on Membership, *not later than*, respectively, April 1 or November 1, all pertinent correspondence and other data together with the record of such applicant's approval or disapproval, with reasons therefor, by the board of membership.

The Committee on Membership shall have custody of such documents so long as needed and then shall deliver them to the custody of the Secretary; they shall remain *confidential*.

The Committee on Membership shall consider the application of each applicant approved for censors' examination by a board of membership. It shall determine finally whether or not such applicant may take that examination.

The Committee on Membership shall not consider the application of any applicant disapproved by a board of membership except on the written request of a majority of that board of membership.

Decisions on applications by the Committee on Membership shall be final, and shall remain in force for two years.

The Committee on Membership shall notify the secretary of the district society concerned and each applicant considered of its decision *not later than*, respectively, April 20 or November 20.

Dr. Fallon pointed out that there were two changes to be noted in this section. The Committee on Membership, rather than the Committee on Medical Education, will take care of all matters pertaining to membership. The local committees on membership, under the setup in vogue at present, have only advisory powers. Under this section as now presented, both the local committee and the central committee have the right to turn down an applicant. He added that there might be times when it would be embarrassing for the local committee to turn down a candidate who, in the opinion of that committee, should be turned down. The decision in such cases can be left to the central committee, and the decision of that committee will be final.

He pointed out that this section contained a further provision to the effect that a candidate once refused admission cannot reapply until two years have elapsed.

Dr. Fallon moved the adoption of Section 2 (c) of Chapter V. The motion was seconded by Dr. Bearse.

Dr. Norman A. Welch, Norfolk, offered the following amendment to Section 2 (c) of Chapter V: insert in line 6 after the word "Membership" the following: "In the case of the rejection of a candidate by the Committee on Membership when said candidate has already been approved by the district committee, this candidate shall have the right of appeal through his district committee to the Executive Committee of the Council. At this hearing the candidate shall be represented by a councilor of his district and the Committee on Membership shall be represented by one of its members." The amendment was seconded by Dr. Bearse.

Dr. Welch supported this amendment by a forceful argument.

Dr. Blaisdell said that the procedure outlined in the amendment would prolong the workings of the committees involved.

Dr. Welch did not agree with the previous speaker. He thought that when somebody is willing to fight it out in favor of a candidate, he should have the right to go to the Executive Committee.

Dr. Henderson expressed his approval of the text as it relates to this section.

Dr. Fallon said that much time had been given to this section. He added that he thought that the by-laws committee had, in it, effected a working compromise between two extremes.

There was a demand for the question. It was put and lost.

The question then came on the adoption of Section 2 (c) of Chapter V, and it was so ordered by vote of the Council.

Dr. Fallon presented Sections 3 and 4 of Chapter V, which read as follows:

*Section 3.* The secretary of each district society shall be the secretary of the district board of censors.

He shall furnish applicants with forms adopted by the Board of Supervising Censors.

He shall keep a record of all applicants for fellowship, and see that each applicant pays the examination fee of three dollars, that this fee is sent *promptly* to the Treasurer, that each successful applicant subscribes to the by-laws and code of ethics and within two weeks pays the assessments for the current year.

He shall furnish each new fellow with a copy of the *Digest, By-laws, Code of Ethics, and Medical Defense Act* of the Society.

He shall present, on the proper form and promptly after each examination, a bill to the Treasurer for censors' services, together with a list of all applicants examined.

The secretary of each district society shall fill out, sign and deliver promptly to the Secretary certificates stating that the successful applicants have complied with the requirements of the by-laws.

*Section 4.* The censors and secretaries shall be paid from the funds of the Society three dollars for each applicant examined. The amount paid shall be divided equally among those officers attending and taking part in the examinations.

Dr. Fallon moved the adoption of Sections 3 and 4 of Chapter V. Dr. Curley seconded the motion.

Dr. Levi offered the following amendment: after the word "ethics" in line 9, insert a period, delete from line 10 the words "and within two weeks pays the assessments for the current year," and add the following sentence: "He shall promptly send the names of successful applicants to the district treasurer, informing him that the assessments must be paid within two weeks, and upon information from the district treasurer, he shall notify the Secretary that all requirements have been fulfilled." He moved the adoption of the amendment. Dr. Bearse seconded the motion.

Dr. Levi spoke, out of his experience as a district secretary, acquired over a period of ten years, in support of the amendment.

Dr. Tully thought that this amendment would complicate the procedure.

The motion was put and lost.

Dr. Stratton offered the following amendment: insert in line 13 of Section 3 of Chapter V, after the words "*Code of Ethics*" the words "of the Society and of the American Medical Association."

Dr. Maclachlan suggested that Dr. Stratton include in his amendment the insertion in line 9, Section 3 of Chapter V, after the word "ethics," the words "of the Society and of the American Medical Association." Dr. Stratton accepted this suggestion; whereupon Dr. Maclachlan seconded the amendment and it was so ordered by vote of the Council.

Dr. Fallon moved the adoption of Section 3 of Chapter V as amended. Dr. Bearse seconded the motion.

Dr. Rice at this point wanted to know why the censors were paid. Dr. Blaisdell answered that it was an old custom.

Dr. Collins asked how much time the censors put in. Dr. Munro answered approximately three hours each year.

Dr. Ober announced that the question before the Council was the adoption of Section 3 of Chapter V as amended. It was so ordered by vote of the Council.

Dr. Fallon moved the deletion of Section 3 of Chapter V of the by-laws as amended in 1941. Dr. Bearse seconded the motion, and it was so ordered by vote of the Council.

Dr. Rice moved that Section 4 of Chapter V of the text be deleted. The motion was seconded by Dr. Collins, and it was so ordered by vote of the Council.

Dr. Bearse presented Chapter VI, Section 1, which reads as follows:

## CHAPTER VI

### OFFICERS

*Section 1.* The President shall preside at the meeting of the Society, of the Council, of the Executive Committee and of the Committee on Public Relations.

He may call a meeting of any committee of the Society.

He shall approve all valid bills against the Society after they have been suitably endorsed by the officer, delegate, or chairman or majority of the committee that has incurred the indebtedness specified in the bill as provided in Chapter VII, Section 1.

He shall sign the certificates of all delegates, at the diplomas of all new fellows if he is satisfied that they have met the requirements of Chapter I.

He shall nominate to the Council all members, committees, all delegates to other medical societies, all fellows to fill vacancies among the officers, censors, censors and commissioners of trial of the Society unless otherwise provided by the by-laws or by order of the Council.

He shall make appointments to fill vacancies *ad interim* in any of the offices of the Society.

He shall be a member *ex officio* of all committees.

He shall, in accordance with specific recommendations by the Committee on Ethics and Discipline, either admonish fellows or appoint a board of trial, as provided in Chapter VIII, Section 1.

He shall report on the state of the Society at the annual meeting.

He shall call one meeting of the Executive Committee between meetings of the Council, and others at his pleasure.

In the event of the death or incapacity of the President-Elect, the President, at the annual meeting of the Council, shall nominate members of standing and special committees, unless otherwise provided in the by-laws.

Dr. Bearse moved the adoption of Section 1 of Chapter VI. The motion was seconded by Dr. H. C. Petterson, Norfolk.

Dr Halbersleben offered the following amendment after line 20, insert the following "He shall nominate no more than one member from one district for any committee" This amendment was seconded by Dr John P. Treanor, Jr, Norfolk. Dr Halbersleben in speaking for the amendment said that it was inspired by a desire to see committee duties spread over the entire state as a means of fostering interest in the Society.

Dr Blaisdell said that, while he was entirely in sympathy with the motives behind the amendment, he was opposed to its inclusion in the by laws. Dr Hornor was likewise opposed.

Dr Halbersleben withdrew his amendment with the consent of the seconder. He offered a new amendment which was just the same as his first with the exception that where the first amendment spoke of one member, the one now offered spoke of two members. This latter amendment was seconded by Dr John C. V. Fisher, Norfolk, and on vote by the Council it was lost.

The question now came on the adoption of Section 1 of Chapter VI. This motion prevailed by vote of the Council.

Dr Bearse moved the deletion of Section 1 of Chapter VI of the by laws as amended in 1941. This motion was seconded by Dr Munro, and it was so ordered by vote of the Council.

Dr Bearse presented Chapter VI, Section 2, which reads as follows:

*Section 2. In the absence of the President the Vice President shall perform the duties of the President and in the absence of both, the senior ex officio Vice President in point of membership in attendance shall perform the duties of the President.*

Dr Bearse moved the adoption of Section 2 of Chapter VI. The motion was seconded by Dr Curley, and it was so ordered by vote of the Council.

Dr Bearse moved the deletion of Section 2 of Chapter VI of the by laws as amended in 1941. Dr Conley seconded the motion, and it was so ordered by vote of the Council.

Dr Bearse presented Section 3 of Chapter VI which reads as follows:

*Section 3. The President Elect shall assist the President in the performance of his duties in such manner as the President may direct and in so doing shall be considered to represent the President.*

At the annual meeting of the Council following the annual meeting at which he was elected, he shall nominate members of standing and special committees unless otherwise provided for in the by laws.

He shall be a member ex officio of all committees.

Dr Bearse moved the adoption of Section 3 of Chapter VI. Dr Conley seconded the motion, and it was so ordered by vote of the Council.

Dr Bearse moved the deletion of Section 3 of Chapter VI of the by laws as amended in 1941. Dr

Chereshkin seconded the motion, and it was so ordered by vote of the Council.

Dr Bearse presented Chapter VI, Section 4, which reads as follows:

*Section 4. The Secretary shall attend all meetings of the Society, the Council and the Executive Committee, and shall record their respective proceedings in separate volumes.*

He shall cause to be engrossed and shall sign the diplomas of new fellows if satisfied that they have met the requirements of Chapter I, and shall issue all diplomas and certificates of fellowship.

He shall notify fellows of votes by the Council or Executive Committee granting permission to retire, to resign, to transfer district membership or to have dues remitted and of votes depriving them of or reinstating them in the privileges of fellowship.

He shall be ex officio secretary of all boards of trial, the Board of Supervising Censors, the Committee on Publications and the Committee on Ethics and Discipline, and shall keep the records of each in separate volumes.

He shall have custody of the seal of the Society and of all books, papers, manuscripts, prints and paintings belonging to the Society except such as are in charge of the Treasurer.

He shall issue notices of the meetings of the Council. He shall issue to every fellow one month before the annual meeting of the Society a program, listing the time and place of that meeting and of the stated meetings of the Council, the boards of censors for that year, and information concerning the payment of assessments and the distribution of publications if there are any proposed amendments to the by laws. He shall provide that each program is accompanied by a copy thereof.

He shall transfer fellows from one district to another under the terms of Chapter III, Section 3, and shall report to the Society at its annual meeting the changes in membership during the year.

He shall conduct official correspondence and shall notify officers, delegates and members of committees of their appointments and of their duties.

He shall keep a directory of the fellows and shall publish the same under the direction of the Committee on Publications at such intervals as may be determined by the Council. He shall furnish this on request to fellows not in arrears.

He shall have jurisdiction over the work of the Executive Secretary.

He shall perform such other duties as the Society or the Council may require.

Dr Bearse moved the adoption of Section 4 of Chapter VI. Dr Fillon seconded it, and it was so ordered by vote of the Council.

Dr Bearse moved the deletion of Section 4 of Chapter VI of the by laws as amended in 1941. Dr Blaisdell seconded the motion, and it was so ordered by vote of the Council.

Dr Bearse presented Chapter VI, Section 5, which reads as follows:

*Section 5. The Treasurer shall collect and care for all monies due the Society and shall have custody of the treasury records. All monies received by any committee, officer or employee on behalf of the Society shall be paid forthwith to the Treasurer.*



He shall be bonded in such sum and manner as may be directed by the Council, on recommendation of the Committee on Finance.

He shall, under the direction of the Council, sue for claims due the Society and shall sell, rent or lease any estate belonging to the Society.

He shall pay only such bills as have been countersigned by the proper officer or delegate, or the chairman or majority of the committee incurring the indebtedness, as provided in Chapter VII, Section 1, and have been approved by the President.

He shall render to the Council at its February meeting a full written report of the assets and liabilities on December 31 of the previous year, and also of the financial transactions of the Society during that year.

He shall attend the meetings of the Committee on Finance, furnish the committee with such data as it may require and shall make all investments and re-investments of the Society's funds, with authority to buy or sell securities subject to the approval of this committee.

He shall arrange for the Cotting luncheons.

He shall familiarize the Assistant Treasurer with the fiscal concerns of the Society.

He shall perform such other duties as the Society or the Council may require.

Dr. Bearse moved the adoption of Section 5 of Chapter VI. The motion was seconded by Dr. Chereskin, and it was so ordered by vote of the Council.

Dr. Bearse moved the deletion of Section 5 of Chapter VI of the by-laws as amended in 1941. Dr. Blaisdell seconded the motion, and it was so ordered by vote of the Council.

Dr. Bearse presented Chapter VI, Section 6, which reads as follows:

*Section 6.* The Assistant Treasurer shall assist the Treasurer in the performance of such duties as the Treasurer may direct.

In the event of the death or the incapacity of the Treasurer, the Assistant Treasurer shall assume the duties of the Treasurer until cessation of the incapacity or the next annual meeting of the Council.

He shall be bonded in such sum and manner as may be directed by the Council, on recommendation of the Committee on Finance.

Dr. Bearse moved the adoption of Section 6 of Chapter VI. Dr. Conley seconded the motion.

Dr. Hornor moved as an amendment that the word "until" be inserted after the word "or" in line 7. This amendment was seconded by Dr. Conley, and it was so ordered by vote of the Council.

Dr. Bearse withdrew his original motion with the consent of the seconder. He moved the adoption of Section 6 of Chapter VI as amended. Dr. Conley seconded the motion, and it was so ordered by vote of the Council.

Dr. Bearse presented Chapter VI, Section 7, which reads as follows:

*Section 7.* The Executive Secretary, under the jurisdiction of the Secretary, shall assist the officers, the

Council and such committees as may request his services.

He shall hold office at the pleasure of the Executive Committee.

Dr. Bearse moved the adoption of Section 7 of Chapter VI. Dr. Conley seconded the motion.

Dr. Rice inquired as to how the Executive Secretary is elected or appointed.

Dr. Ober answered by saying that he is elected by the Executive Committee of the Council.

Dr. Rice inquired why he should not work under the direction of that committee. "It says here," he added, "that the Secretary shall have jurisdiction over the work of the Executive Secretary." He further commented that the Executive Secretary would not know for whom he was working.

Dr. Fallon, in response, said that that was just the reason that the committee decided to do things in this way. He added that in the past the Executive Secretary did not know for whom he was working. Furthermore, the committee felt that the responsibility for his work should be centralized.

There was a demand for the question from several sources.

Dr. Ober put the motion, and it was so ordered by vote of the Council.

Dr. Bearse moved the deletion of Section 6 of Chapter VI of the by-laws as amended in 1941. Dr. Fallon seconded the motion, and it was so ordered by vote of the Council.

Dr. Bearse presented Chapter VI, Section 8, which reads as follows:

*Section 8.* The traveling and incidental expenses of the officers and committees elected by districts and of standing committees of the Society, on request, shall be paid by the Treasurer, on presentation of an itemized bill duly approved by the President.

Dr. Bearse moved the adoption of Section 8 of Chapter VI. This motion was seconded by Dr. Fallon.

Dr. Curley moved as an amendment that in line 2, after the word "committees," there be inserted the words "of the Society." Dr. Fallon seconded the amendment, and it was so ordered by vote of the Council.

Dr. Bearse, with the consent of the seconder, withdrew his original motion to adopt Section 8 of Chapter VI. He moved the adoption of Section 8 of Chapter VI as amended. Dr. Conley seconded the motion and it was so ordered by vote of the Council.

Dr. Bearse moved the deletion of Section 7 of Chapter VI of the by-laws as amended in 1941. Dr. Fallon seconded the motion, and it was so ordered by vote of the Council.

Dr Blaisdell asked the unanimous consent of the Council to reconsider the vote by which Section 4 of Chapter VII was adopted. On a vote this consent was given.

Dr Blaisdell moved that, in line 2 of Section 4 of Chapter VII, the word "fellow" be deleted and the word "councilor" substituted. Dr Fallon seconded the motion, and it was so ordered by vote of the Council.

Dr Blaisdell moved the adoption of Section 4 of Chapter VII as amended. Dr Fallon seconded the motion, and it was so ordered by vote of the Council.

Dr Fallon presented Section 1 of Chapter VIII, which reads as follows:

### CHAPTER VIII

#### BOARDS OF TRIAL

*Section 1* A board of trial shall consist of five of the commissioners of trial, appointed by the President to consider charges against a fellow recommended for trial by the Committee on Ethics and Discipline.

The President shall designate a time and place for the meeting of such board, and shall cause due notice thereof to be given to the complainants and to the accused and to all members of the district society of which the accused is a member.

A board of trial may hear fellows who appear in the interest of the accused but legal counsel shall be excluded.

Failure of the accused to appear or be represented at the trial shall be considered *prima facie* evidence of the truth of the charges, and a verdict may be rendered accordingly. In case of conviction, a board shall recommend such sentence as it shall deem best as provided in Chapter I Section 10. The Secretary shall enter on the records the proceedings of each board of trial and shall report them to the Society at the next annual meeting for final action.

The Secretary shall notify the accused of the findings of a board of trial and of the action of the Society thereon and he shall notify the several district societies of the sentence imposed.

Dr Fallon moved the adoption of Section 1 of Chapter VIII. The motion was seconded by Dr Blaisdell, and it was so ordered by vote of the Council.

Dr Fallon moved the deletion of Section 1 of Chapter VIII of the by laws as amended in 1941. Dr Rice seconded the motion, and it was so ordered by vote of the Council.

Dr Fallon presented Section 2 of Chapter VIII which reads as follows:

*Section 2* Each commissioner, and each prosecuting officer shall be paid ten dollars a day for attendance plus his incidental expenses.

It shall be a duty of any fellow summoned by the Committee on Ethics and Discipline to appear as a witness before a board of trial. No fellow shall be relieved of this duty without an excuse satisfactory to such a board.

Dr Fallon moved the adoption of Section 2 of Chapter VIII. Dr Harold G Giddings, Middlesex South, seconded the motion, and it was so ordered by vote of the Council.

Dr Fallon moved the deletion of Section 2 of Chapter VIII of the by laws as amended in 1941. Dr Bearse seconded the motion, and it was so ordered by vote of the Council.

Dr Blaisdell presented Chapter IX which reads as follows:

### CHAPTER IX

#### AMENDMENTS

These by laws may be amended by a majority vote at any annual meeting of the Society, provided the proposed amendment or amendments shall have been submitted previously in writing to the Council, shall have been approved by that body by vote and shall have been published and forwarded to each fellow, along with the program of the meeting of the Society whereat they are to be considered.

Dr Blaisdell moved the adoption of Chapter IX. Dr Bearse seconded the motion, and it was so ordered by vote of the Council.

Dr Blaisdell moved the deletion of Chapter IX of the by laws as amended in 1941. Dr Fallon seconded the motion, and it was so ordered by vote of the Council.

Dr Blaisdell moved the adoption of the report of the committee as a whole with the respective amendments thereto. Dr Hornor seconded the motion, and it was so ordered by vote of the Council.

Dr Bagnall moved that the Council extend a rising vote of thanks to the committee for this work. The motion was seconded by Dr Charles J Kichham, and it was so ordered amidst great applause.

Dr Blaisdell moved that the meeting adjourn. This motion was seconded by Dr Bearse and carried, after Dr Ober had expressed his thanks to all who had seen the session through.

Adjournment was at 5.30 p.m.

MICHAEL A TIGHE, *Secretary*

### APPENDIX NO 1

#### ATTENDANCE

BARNSTABLE	R M Chambers
D E Higgins	J A Reese
	W H Swift
BERKSHIRE	BRISTOL SOUTH
J J Boland	E D Gardner
C F Kernan	C C Tripp
BRISTOL NORTH	ESSEX NORTH
W H Allen	E S Bagnall
J H Brewster	E H Ganley

H. R. Kurth  
P. J. Look  
R. C. Norris  
G. L. Richardson  
A. F. Shea  
F. W. Snow  
T. N. Stone  
C. F. Warren

## ESSEX SOUTH

R. E. Foss  
Loring Grimes  
P. P. Johnson  
O. S. Pettingill  
W. G. Phippen  
E. D. Reynolds  
J. R. Shaughnessy  
C. F. Twomey

## FRANKLIN

W. J. Pelletier  
H. G. Stetson  
A. H. Wright

## HAMPDEN

E. P. Bagg  
W. C. Barnes  
J. L. Chereskin  
E. C. Dubois  
P. E. Gear  
G. D. Henderson  
A. G. Ricé  
G. L. Steele

## HAMPSHIRE

J. R. Hobbs  
Mary P. Snook

## MIDDLESEX EAST

J. H. Blaisdell  
Richard Dutton  
E. M. Halligan  
J. H. Kerrigan  
K. L. MacLachlan  
R. R. Stratton  
J. M. Wilcox

## MIDDLESEX NORTH

H. R. Coburn  
W. M. Collins  
R. L. Drapeau

A. R. Gardner  
W. H. Sherman  
M. A. Tighe

## MIDDLESEX SOUTH

C. F. Atwood  
E. W. Barron  
W. B. Bartlett  
Harris Bass  
R. W. Buck  
E. J. Butler  
B. F. Conley  
D. F. Cummings  
H. F. Day  
J. G. Downing  
A. W. Dudley  
C. W. Finnerty  
H. G. Giddings  
H. W. Godfrey  
Eliot Hubbard, Jr.  
A. M. Jackson  
A. A. Levi  
F. P. Lowry  
A. N. Makechnie  
R. A. McCarty  
J. C. Merriam  
C. E. Mongan  
J. P. Nelligan  
Dwight O'Hara  
L. S. Pilcher  
E. H. Robbins  
W. D. Roche  
E. F. Ryan  
E. F. Sewall  
J. E. Vance  
Hovhannes Zovickian

## NORFOLK

Carl Bearse  
L. F. Curran  
F. P. Denny  
Albert Ehrenfried  
J. E. Fish  
J. C. V. Fisher  
Susannah Friedman  
David Glunts  
B. T. Guild  
D. L. Halbersleben  
J. B. Hall  
R. J. Heffernan  
I. R. Jankelson

H. L. Johnson  
C. J. Kickham  
C. J. E. Kickham  
E. L. Kickham  
D. L. Lionberger  
D. S. Luce  
T. F. P. Lyons  
F. P. McCarthy  
R. T. Monroe  
F. J. Moran  
M. W. O'Connell  
H. C. Peterson  
Frederick Reis  
S. A. Robins  
S. M. Saltz  
D. D. Scannell  
J. A. Seth  
J. W. Spellman  
M. H. Spellman  
J. P. Treanor, Jr.  
W. J. Walton  
N. A. Welch

## NORFOLK SOUTH

C. S. Adams  
H. H. A. Blyth  
F. W. Crawford  
W. G. Curtis  
D. B. Reardon  
W. L. Sargent

## PLYMOUTH

J. E. Brady  
Charles Hammond  
W. T. Hanson  
P. B. Kelly  
P. H. Leavitt  
D. W. Pope  
W. H. Pulsifer

## SUFFOLK

H. L. Albright  
A. W. Allen  
W. B. Breed  
W. E. Browne  
C. S. Butler  
G. C. Caner  
E. M. Chapman  
David Cheever  
Pasquale Costanza  
R. L. DeNormandie

N. W. Faxon  
G. B. Fenwick  
Maurice Fremont-Smith  
Channing Frothingham  
Joseph Garland  
John Homans  
A. A. Hornor  
C. S. Keefer  
H. A. Kelly  
C. C. Lund  
H. C. Marble  
W. J. Mixter  
Donald Munro  
H. L. Musgrave  
R. N. Nye  
F. R. Ober  
J. P. O'Hare  
W. T. O'Halloran  
L. E. Parkins  
L. E. Phaneuf  
Helen S. Pittman  
R. M. Smith  
E. F. Timmins  
S. N. Vose  
Shields Warren  
Conrad Wesselhoeft

## WORCESTER

J. C. Austin  
Gordon Berry  
W. P. Bowers  
L. R. Bragg  
G. A. Dix  
J. M. Fallon  
L. M. Felton  
E. L. Hunt  
E. R. Leib  
W. F. Lynch  
A. W. Marsh  
J. C. McCann  
R. S. Perkins  
G. C. Tully  
R. J. Ward

## WORCESTER NORTH

H. C. Arey  
E. A. Adams  
J. J. Curley  
C. B. Gay  
J. C. Hales

# CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTE-MORTEM AND POST-MORTEM RECORDS AS USED  
IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

## CASE 28201

### PRESENTATION OF CASE

A thirty-seven-year-old French-Canadian shoe-worker was admitted to the hospital because of hoarseness, cough and dysphagia.

The patient was in good health until about thirteen months before entry, when there was insidious onset of cough. Two months later, after a bout of coughing, he suddenly became so hoarse that he was barely able to talk. Although this acute aphonia soon passed, the patient remained slightly hoarse from then on. In the eight months before entry, he had a paroxysmal cough, productive of thick greenish sputum. Five weeks before entry, there was sudden onset of dysphagia, solid foods seeming to stick in the throat at the level of the thyroid cartilage. During the period of all of these symptoms, there was also insidious appearance of slight dyspnea on exertion, loss of 12 pounds of weight and increased nervousness.

The family history was irrelevant. There was no known exposure to tuberculosis. The patient had had a mastoidectomy seven years before entry, with residual deafness in the right ear. He had urethral discharge on two occasions, twelve and seven years before entry.

On admission, the patient appeared well developed and nourished. Hearing was diminished in the right ear, and a right mastoid scar was present. The tonsils were absent. The left vocal cord lay in the midline, and was paralyzed; the right cord was normal. The trachea was deviated slightly to the right. The lungs were clear, and the heart seemed normal. The abdomen was normal.

The blood pressure was 110 systolic, 70 diastolic. The temperature was 98.6°F., the pulse 80, and the respirations 20.

Examination of the blood showed a red-cell count of 5,020,000 with 13 gm. hemoglobin, and a white-cell count of 8100 with 69 per cent polymorphonuclears. The blood Hinton reaction was negative. The sedimentation rate was 1.6 mm. per minute. The urine and stools were normal. A tuberculin test was positive, in a dilution of 1:50,000.

A roentgenogram of the chest with a barium swallow showed a mass in the upper mediastinum, just behind the sternum and above the arch of the

aorta. The esophagus was narrowed, particularly posteriorly at an area, about 4 cm. long, just above the upper edge of the aortic arch. The mucosa appeared destroyed in the area of narrowing. The lung fields were clear.

On the seventh hospital day, bronchoscopy was performed. The left vocal cord was found to be paralyzed. The carina appeared markedly thickened, reddened, irregular and fixed. In the region of the right upper-lobe bronchial orifice, there was an irregular, reddened thickened mass. The right middle and lower bronchial orifices seemed normal. There was an irregular, reddened outcropping mass in the left main bronchus, producing obstruction. Biopsies from the carina, from the right and from the left bronchi showed acute and chronic inflammation, with necrosis and granulation tissue.

Three days later, esophagoscopy was performed, showing no evidence of extrinsic pressure and no mucosal abnormality, except for a slightly granular, questionably polypoid area about 30 cm. distant from the upper incisors. This level was considered to be somewhat below that of the lesion described in the roentgenogram. Biopsy of this area showed no diagnostic abnormality.

Five days later, a small axillary lymph node was removed for biopsy. Sections showed hyperplasia.

In the next two weeks, the patient was given a total of 1200 r of x-ray to the anterior mediastinum, and 1100 r to the posterior mediastinum. Following this, a roentgenogram of the chest showed no change in the mass in the upper mediastinum. There seemed to be definite involvement of the wall of the esophagus.

The patient was discharged unimproved, and was followed in the Out Patient Department. Three weeks later, a roentgenogram of the chest again showed no change in the mediastinal mass. There was constant irregular narrowing of the esophagus in the area previously described, apparently due to an intrinsic lesion. A week later, bronchoscopy and esophagoscopy were again performed.

### DIFFERENTIAL DIAGNOSIS

DR. EDWARD D. CHURCHILL: "The left vocal cord lay in the midline, and was paralyzed." From that item of the examination, we go back to the episode in the history, eleven months previously, of a bout of coughing, hoarseness and a period of acute aphonia. Paralysis of one vocal cord need not give hoarseness and does not cause acute aphonia. Consequently, we have no right to infer that the left vocal-cord paralysis came on eleven months previously. I bring that up as an important consideration because, with vocal-cord

paralysis due to cancer, other manifestations of that cancer might well be expected in eleven months.

The sedimentation rate, although not corrected, was elevated. How many adults thirty-seven years of age, Dr. King, show a positive tuberculin reaction in a dilution of 1:50,000 without active disease?

DR. DONALD S. KING: I think plenty of them do.

DR. CHURCHILL: Then, the positive test in high dilution is not significant?

DR. KING: No; I do not believe so. I show a strong reaction in a dilution of 1:100,000 myself.

DR. CHURCHILL: But you are in daily contact with patients with positive sputum.

DR. KING: Yes; but I do not have active disease.

DR. CHURCHILL: Dr. Hampton, can you show us the mass in the upper mediastinum beneath the sternum above the arch of the aorta?

DR. AUBREY O. HAMPTON: At the arch of the aorta, there is a pressure defect behind the esophagus and sternum, pressing on the esophagus here.

DR. CHURCHILL: But quite a distance from the sternum?

DR. HAMPTON: I think it was quite intimate with the esophagus.

DR. CHURCHILL: But not a substernal mass?

DR. HAMPTON: No; not between the trachea and sternum. It is at the right margin of the esophagus and posterior; I should say that it is a prevertebral mass.

DR. CHURCHILL: That is quite a different interpretation. Certainly, there was enough evidence to go ahead with esophagoscopy and, possibly, also bronchoscopy because of the cough and sputum. The left vocal-cord paralysis was confirmed, and the carina of the trachea was thickened, reddened and fixed. In the right upper-lobe orifice, there was an irregular thickened, reddened mass, and on the left side the same thing but with an outcropping in the bronchus. The definition of outcropping is "tissue without an intact mucous-membrane covering." The endoscopist differed sharply with the radiologist because he said that the esophagus showed no evidence of extrinsic pressure and no mucosal abnormality except for a slightly granular, questionably polypoid area about 30 cm. distant from the upper incisors.

Dr. Benedict, where is 30 cm. from the upper incisors? Tell me when I reach it on this film.

DR. EDWARD B. BENEDICT: About 15 cm. above the diaphragm.

DR. CHURCHILL: Not in the region of the mass! At this point, just above the diaphragm, the questionable polypoid area was observed and a biopsy taken, but no microscopic abnormality was recognized. In other words, the endoscopist did not see any abnormality until this low level was reached

and then found something indefinite and not significant. It is obvious that a diagnosis of either lymphoma or cancer was entertained because the patient was given x-ray therapy—1200 r to the anterior mediastinum, and 1100 r to the posterior. This I assume to be in the diagnostic range rather than full therapy. Is that correct?

DR. HAMPTON: A sensitive carcinoma dose, larger than the usual lymphoma dose, was given because it was thought that the gastrointestinal tract was involved, and growths in that region require heavier dosages than the average.

DR. TRACY B. MALLORY: The X-ray Department frankly suggested that it be given as a diagnostic measure.

DR. CHURCHILL: The mass did not change. Again, the X-ray Department stated that there was definite involvement of the wall of the esophagus. Three weeks later, there was still no change in the mass, and it was therefore proved not to be a radiosensitive tumor.

Again, the roentgenologists stated very emphatically, "due to an intrinsic lesion." They became more and more emphatic as the irritation of the report of the endoscopist reached them. Then the esophagoscopist got irritated in turn, and he did both bronchoscopy and esophagoscopy. This, I take it, settled the matter.

Dr. Hampton, do you still believe just as emphatically that this represents both extrinsic deformity and intrinsic involvement of the mucosa of the esophagus?

DR. HAMPTON: The radiologist considered that the wall of the esophagus was certainly involved. Whether in the beginning the mucosa was involved, I do not know, but that is the picture of a mass in the wall of the esophagus. We may have become a little more emphatic because of this film at a later examination in which the mucosa does look definitely involved.

DR. CHURCHILL: Which side is this?

DR. HAMPTON: The left.

DR. CHURCHILL: The left recurrent nerve again!

DR. HAMPTON: Yes; there is a suggestion of prominence, but I cannot be sure of it. It may be that the mediastinal tissues are pushed over. It may be that there is no pressure on the esophagus here. I cannot be sure there is anything where the recurrent laryngeal nerve is.

DR. CHURCHILL: There are two or three things to decide. Going back to the problem of recurrent-nerve paralysis, in the absence of aneurysm, this almost invariably means cancer. I think we have seen one case of pulmonary tuberculosis with recurrent-nerve paralysis. Is that so, Dr. King?

DR. KING: I do not remember the verification of it. We have not got one that I am sure of.

ere is one where we thought the x-ray evidence s good

Dr CHURCHILL: There is no enlargement of the : auricle?

Dr HAMPTON. No.

Dr CHURCHILL: We come down, I should say, discounting the history of the period of acute monia and conclude that at some time a left urrent nerve paralysis occurred. It could have urred at any time within the previous eleven nths, but not necessarily so long ago. Did the ore than lymphoma" dosage and re-examination ee weeks later reveal any change?

Dr HAMPTON: If anything, it was worse.

Dr CHURCHILL. I shall rule out lymphoma, ich is a radiosensitive tumor.

Let us leave neoplasm and go back to the possi- ty of tuberculosis, because of this strange find- g of a mass partially obstructing the right upper e bronchus and an outcropping mass obstruct- g the left. It is very difficult to link up that iding with the chest film. No films were taken nspiration and expiration, but I doubt whether ey are needed.

Dr HAMPTON: The lungs certainly do not look ry emphysematous. In the oblique view, one n see the right main bronchus to this point, and e right upper-lobe bronchi are not seen, prob- ly because they are projected on end. The left ain bronchus is seen up to the point where the ophagus covers it. There is no mass right in that ea, which must be beyond the carina.

Dr BENEDICT: In my bronchoscopic report, I d not say complete obstruction; I said partial nstruction of the left.

Dr CHURCHILL: Could this be the endobron- al type of tuberculosis? Information about the ick greenish sputum that the patient was raising as been withheld. I do not know why he was using it from the lung unless from bronchial nitation. Certainly, with thick greenish sputum nd a bilateral endobronchial lesion, we are ent- led to know whether the sputum was positive

Dr MALLORY: The sputum was examined twice nd reported negative for tubercle bacilli

Dr CHURCHILL. Could the distortion of the ophagus have been due to a tuberculous lymph ode secondary to the bronchial lesion? I think it nlikely and rule out endobronchial tuberculosis s a likely possibility.

That brings us back to neoplasm. Certainly, I ee little evidence on which a diagnosis of primary arcinoma of the lungs can be based. Conceivably, small cancer might exist in the periphery of the ung invading the mediastinum, with lymph node nvolvevement. But a cancer that is outcropping in, he bronchus would have yielded a positive biopsy, nd also would have produced some obstruction in

at least one of the segmental bronchi of the upper lobe.

I am going to cast my lot with the X-ray De- partment, and say that until proved otherwise, this mass be considered primary cancer of the esophagus, with direct extension into the left primary bronchus and perhaps with lymph node metastases causing distortion of the carina and invasion of the left recurrent nerve

Dr KING. We had one case, Dr. Churchill, that showed tuberculosis of the wall of the esophagus. Of course, since tuberculosis would not involve the bronchus in the same way, we can discard that diagnosis.

Dr. HAMPTON. If you could believe absolutely that these first films show only a submucosal intramural lesion, what should you think?

Dr CHURCHILL. That question brings us back to the old question whether cancer of the esopha- gus can start in the deep layers and not show mucosal ulceration. We thought that some ten years ago, but now I wonder what we were seeing. In other words, I shall doubt the existence of that entity until I see it again, because our older observa- tions were not too well supported.

Are you ready to call it cancer of the esophagus by x-ray examination?

Dr HAMPTON. I should say that whatever the disease was, it was invading the esophagus, and there are not many things that will invade the esophagus. I think there is one possibility, other than cancer.

Dr MALLORY. Do you want to tell us that, Dr. Hampton?

Dr HAMPTON. I thought Dr. King was going to. It is mediastinal tuberculosis, with perforation of the esophagus

Dr MALLORY. Dr. Benedict, you might describe the final endoscopy.

Dr BENEDICT. The second bronchoscopy con- firmed the first bronchoscopy. There was exactly the same appearance, with a mass of reddened inflammatory tissue involving the carina, left main bronchus and right main bronchus in the region of the upper lobe. The esophagoscopy did show, on second examination, extrinsic pressure pushing the esophagus forward, but definitely no mucosal involvement.

Dr. HAMPTON: Not even edema?

Dr BENEDICT: No

Dr HAMPTON. Edema could explain the x-ray picture satisfactorily.

Dr LOWREY F. DAVENPORT. Does not the char- acter of the symptoms disturb you with that diagnosis?

Dr CHURCHILL. You mean cough and sputum, then the hoarseness and then the dysphagia? Yes; it points toward lung rather than esophagus

DR. MALLORY: Although we have seen just that with cancer of the esophagus.

DR. KING: Since we have raised the question of tuberculosis, have you ever seen tuberculosis of the bronchus with this story and these physical signs?

DR. DAVENPORT: No.

DR. KING: It is hard to imagine that, even if the lymph node perforated through into the bronchus. It is the first case of this sort that we have seen.

DR. HAMPTON: We have seen cancer of the breast metastasize to the mediastinum and esophagus in this way. I do not see why a tuberculous lymph node could not do the same thing. Such a case was reported in this conference, but we examined the esophagus by x-ray and found nothing. The patient died of tuberculous mediastinitis, which perforated into the esophagus.

#### CLINICAL DIAGNOSIS

Mediastinal tumor (? pulmonary or esophageal carcinoma).

#### DR. CHURCHILL'S DIAGNOSIS

Carcinoma of the esophagus, with extension to bronchus and regional lymph-node metastases.

#### ANATOMICAL DIAGNOSIS

Tuberculosis of bronchus.

#### PATHOLOGICAL DISCUSSION

DR. MALLORY: On the final endoscopic examination, no change in the esophagus was noted. More biopsies were taken, and this time it was possible to make a positive diagnosis of tuberculosis of the bronchus. We could only guess the rest, but I should think that there was mediastinal tuberculosis, pressing on the esophagus and very probably invading the recurrent laryngeal nerve.

### CASE 28202

#### PRESENTATION OF CASE

A fifty-two-year-old lawyer was admitted to the hospital because of a "heart attack" on the preceding day.

The patient was in good health until three years before entry, when there was insidious onset of nervousness and fatigue and a sense of lifeless depression following work. At this time, there also appeared a sense of constriction in the back of the neck, which was relieved by osteopathic treatment. The patient also experienced occasional mild shooting pain in the region of the left nipple but had no substernal pain or shortness of breath. He consulted a physician, who found his heart slightly enlarged to the left with regular sounds of good quality. The aortic second sound was greater than

the pulmonic, and there were no significant murmurs. The lungs were clear and full. Physical examination was otherwise negative. The blood pressure was 184 systolic, 120 diastolic, on one examination and 162 systolic, 110 diastolic, on another. The Hinton reaction of the blood was negative, and the nonprotein nitrogen level was 30 mg. per 100 cc. The urine was normal. A roentgenogram of the chest showed that the heart was just slightly enlarged in all its diameters. The great vessels were rather dense and tortuous but showed no evidence of aneurysm. Their appearance suggested an aortitis. There was scoliosis of the dorsal spine, with convexity to the left in the lower portion and to the right in the upper portion. General relaxation was recommended by the physician. The patient remained fairly well for the following three years, complaining occasionally of fatigue. His wife stated that he had been under a nervous strain because of business worries.

On the day before entry, while fighting a brush fire with others of his family, the patient suddenly said to his wife, "I am having a heart attack; I am dying," and slumped to the ground. He was taken to his house temporarily. He was unconscious and very restless, and breathing was difficult, with long periods of apnea. According to his wife and physician, he seemed to suffer no pain. The following day, his breathing was better, and he was taken to the hospital, approximately twenty-four hours after the onset of the attack.

On admission, the patient was semistuporous, with poor color, and was breathing irregularly. Heart sounds were of poor quality but were regular. A systolic murmur was audible over the precordium, with transmission into the axilla. The radial arteries were tortuous and palpable. The extremities were warm. The nailbeds and lips were moderately cyanotic. The veins of the neck were not distended.

The blood pressure was 60 systolic, 40 diastolic. The temperature was 100.5°F., the pulse 75, and the respirations 20.

The blood Hinton reaction was negative, and the blood nonprotein nitrogen was 65 mg. per 100 cc.

An electrocardiogram showed absence of R<sub>4</sub> and unusually high T waves, with concave upstroke in Leads 2 and 3. There was moderate left-axis deviation and normal rhythm, with a rate of 120. All leads showed upright T waves.

The patient was given morphine. He continued restless and cyanotic. Although he passed no urine, his bladder did not become distended. He had not voided since the onset of the attack, but catheterization twelve hours after onset yielded

90 cc. of urine. The following morning, respiration was stertorous, with tracheal rales and intermittent periods of apnea. The blood pressure was 70 systolic, 40 diastolic, and the pulse was 100 and regular. At no time did the patient complain of pain. Death occurred twenty-two hours after admission.

### DIFFERENTIAL DIAGNOSIS

Dr. EDWARD F. BLAND: This case presents a rather unusual combination of symptoms and signs: stupor, hypotension and a relatively slow pulse. The only thing that seems reasonably certain is that there must have been a vascular accident somewhere; the question is, Was it in the central nervous system or the coronary circulation, or did it involve some other organ? The first thing that is striking is that the patient became quickly stuporous or unconscious following some sort of discomfort in the chest, and I assume from the record that he remained more or less stuporous until the time of death. Another striking feature is the blood pressure, which was low in the absence of the usual signs of peripheral shock: the patient was warm, and the pulse was not fast. The pulse does not have to be fast with peripheral circulatory collapse but it usually is, so that this combination of stupor, low blood pressure and relatively slow pulse is a bit difficult to fit together. We have a little freedom in connection with the pulse, however, because when the patient was first admitted it was said to be 75 and then later on, not long before death, it was 100. Somewhere in between, it got up to 120 by electrocardiogram.

Did this patient have a subarachnoid hemorrhage? I do not believe so. The absence of headache at the beginning, although a little unusual, does not exclude it, but it would be difficult to account for the extreme hypotension on this score. Furthermore, since we are given no information about stiffness of the neck, I think we can assume that it was not present, and there were no neurologic signs. Therefore, if we assume that this was not a subarachnoid hemorrhage, or some vascular accident in the central nervous system, we must account for the stupor on some other score. Perhaps I am overemphasizing the unconscious state. Am I, Dr. Smith?

Dr. WILLIAM D. SMITH: Just a bit.

Dr. BLAND: The next most striking feature seemed to be the extremely low blood pressure, which remained thus until death. It could be due to a number of conditions.

The abrupt onset promptly brings to mind dissecting aortic aneurysm, which, furthermore, comes on with unusual exertion. Whether the patient actually had pain in the chest seems uncertain,

but it could not have been a very striking symptom. Something, however, must have happened in the chest. At least, the patient's attention was temporarily directed, so long as he was conscious, to his chest. If this were an aortic dissection, and we know that dissecting aneurysm can do bizarre things, the first thing we find difficulty in accounting for is the hypotension. It is conceivable, and such an event has been recorded, that the dissection involved the mouths of both subclavian vessels, which might give one a false reading of hypotension in the arms, but we must still account for the stupor, which I must assume was due to the extremely low blood pressure. This, in turn, probably accounted for the failure of the kidneys to secrete urine and for the rising nonprotein nitrogen. Dissecting aneurysm could do all these things, but this would hardly be consistent with two days of life without some other suggestive evidence indicating a serious interference with the circulation to the lower extremities. Therefore, I cannot make a diagnosis of dissecting aneurysm of the aorta.

Finally, Did this patient have a relatively painless but large myocardial infarct? I am inclined to think that this is the most likely explanation, but I am not very happy with that diagnosis either. We do see now and then, of course, an extremely low blood pressure following a large myocardial infarct, and in some cases infarcts at the base of the heart are associated with a relatively slow pulse, since vascular lesions at the base of the heart are more apt to disturb also the circulation to the auricles than lesions responsible for apical infarcts. At this point, I think the electrocardiogram might be a good deal of help, and I should like to see the tracing, since I am suspicious of the high concave T waves in Leads 2 and 3 mentioned in the record, because shortly after a large myocardial infarct at the base of the heart, the waves might be large and high. After seeing the tracing shown here on the screen, I am disappointed. All this film shows is a left-axis deviation of moderate degree, a full length PR interval up to 0.19 second, upright T waves, more or less normal shape in Leads 2 and 3 and a chest lead that shows a very minute R wave, possibly absent. I had hoped for more positive help from the electrocardiogram pointing to myocardial infarction; instead, it casts a good deal of doubt on the correctness of this diagnosis. Therefore, one begins to think in terms of something more unusual and hence less likely. This low blood pressure could be due, of course, to constriction of the heart. It could be due to obstruction to the circulation inside the heart—for example, by a thrombus, which is usually formed in the presence of considerable valvular disease,



notably mitral stenosis. I have not seen it in any other situation. The other condition that might account for the low blood pressure is cardiac tamponade, but we are specifically told that the veins were not distended; therefore, this possibility is untenable.

So far as various unlikely possibilities are concerned, there occasionally has been described a syndrome with extreme hypotension and collapse in connection with bilateral hemorrhage in the adrenal glands. In the course of serious infection in childhood, hemorrhage may occur into both adrenal glands, with symptoms resembling acute Addison's disease. Dr. Grantley W. Taylor,\* some years ago, described such a case of bilateral hemorrhage into both adrenal glands following an operation. The patient went into collapse, stupor and hypotension, and died. Death was not explained until the post-mortem examination, when the bilateral apoplexy of the adrenal glands was found. I cannot fit that into this picture.

In summary, I am left with myocardial infarction, in spite of the relatively normal electrocardiogram, as my choice of the three most likely diagnoses noted above,—the other two being subarachnoid hemorrhage and dissecting aneurysm,—and I should explain the renal failure and the cloudiness of the sensorium as secondary to the critically low blood pressure.

DR. TRACY B. MALLORY: Does anyone want to champion any of the other possibilities Dr. Bland has mentioned?

DR. PAUL D. WHITE: The patient did not have characteristic electrocardiographic evidence of acute myocardial infarction. In a patient so sick, there should be more definite findings of acute coronary occlusion than absence of R<sub>4</sub> alone, which might be due to a faulty position of the electrode or to an old infarct. We should expect greater changes in the ST segment in at least one of these four leads, if he was so sick from myocardial infarction alone.

DR. BLAND: Yes; that is the most serious objection to myocardial infarction.

DR. SMITH: I came to the same diagnosis that Dr. Bland came to but less logically. There were various things that I did not consider at all. I ruled out dissecting aneurysm in the first place on the entire absence of pain, and I tried very hard to get a story of pain. We asked the patient's wife if she thought that he had had pain. She said, "No." I telephoned the local doctor, who also said that the patient had had no pain. Dissecting aneurysm without pain was something outside my experience. Another thing that influenced me against it was the low blood pressure, because generally the blood

pressure is tolerably well maintained in dissecting aneurysm. I therefore came to the same clinical diagnosis as Dr. Bland.

DR. EARLE GLENDY: When was the first blood-pressure reading made in relation to the onset?

DR. SMITH: As soon as the patient came in to the hospital, which was twenty-four hours after the onset.

DR. GLENDY: With massive dissection of the aorta, it is possible for the coils of the dissected inner portion of the aorta to occlude the aorta; then the blood pressure falls very rapidly, and the heart fails.

DR. SMITH: The patient did not impress me as having heart failure.

DR. F. DENNETTE ADAMS: Did he not have shock?

DR. SMITH: Yes; we gave oxygen and morphine.

DR. ADAMS: Then, why did he not have dissecting aneurysm? They ordinarily do not rupture in the absence of pain, but he perhaps had stupor, or relative stupor before he had an opportunity to tell about it.

DR. WHITE: I should like to emphasize that last statement of Dr. Adams. I have been caught out here several times by the absence of pain in patients with vascular shock. This patient did, however, have enough pain in the beginning to think he had a "heart attack." At least, figuratively, he put his hand to his chest; what he felt was bad enough to make him think he was going to die. Whether he had coronary thrombosis or dissecting aneurysm, I believe he had sudden and severe chest pain at the very beginning before he collapsed; the very abruptness favors somewhat dissection of the aortic wall.

#### CLINICAL DIAGNOSES

Hypertensive and coronary heart disease.  
Myocardial infarct.

#### DR. BLAND'S DIAGNOSES

Coronary thrombosis.  
Myocardial infarction.

#### ANATOMICAL DIAGNOSES

Dissecting aneurysm of aorta, with slight hemorrhage into mediastinum, pericardium and pleural cavities.  
Pulmonary edema.  
Hemorrhage into lungs.  
Hypertrophy of heart, hypertensive type.  
Subepicardial and subendocardial hemorrhage, both auricles.  
Arteriosclerosis of aorta and of coronary and pulmonary arteries, moderate.  
Acute focal myocardial infarction.

\*Taylor, G. W. Intestinal diverticulosis, pernicious anemia, bilateral suprarenal apoplexy: report of a case. *New Eng. J. Med.* 202:269-271, 1930.

## PATHOLOGICAL DISCUSSION

DR. MALLORY: At autopsy, the first thing evident was that the ascending aorta and arch were swollen and bright red. Dissecting gingerly into his area, we found a tube filled with partially clotted blood and then inside it was another tube consisting of the inner half of the aortic wall. The dissection was complete from the level of the coronary mouths down to the bifurcation of the aorta and some distance into each iliac artery; it had re-entered the right iliac but not the left. There was also dissection some distance down the superior mesenteric artery, the adrenal arteries, both subclavians, both carotids and a minute portion of the splenic.

DR. WHITE: Not in the coronaries?

DR. MALLORY: No; we could not make out any dissection in the coronaries. There was blood around the mouths of both coronaries, but in each instance it seemed to be external to the wall of the artery. About 3 cm. above the aortic cusps was an almost complete transverse tear of the aorta. A second tear was also present, running almost at right angles to the first one down to a point only 3 mm. from the mouth of the right coronary artery. There was no atheroma in the ascending portion of the aorta in the region of the tear. It began in the region of the arch and became progressively more severe as one passed down to the iliacs. From the gross examination, it looked as if the mesenteric artery had been definitely occluded by the dissection, but the intestines were not infarcted, so that if occlusion were ever complete, it could not have

been present for any significant period. The coronary arteries, in contrast, did not seem to be occluded, but sections of the myocardium showed innumerable small foci of acute necrosis throughout the entire left ventricle. There was, in effect, almost total infarction.

DR. WHITE: That would have to be two days old for one to see it?

DR. MALLORY: Yes; an extremely acute change—as yet no leukocytic reaction but a definite change in the staining of the muscle fibers, and also a slight change in the character of the nuclei of the endothelial cells in the immediate region of each focus.

DR. BLAND: Therefore, the process was there when the electrocardiogram was taken.

DR. MALLORY: Yes.

There were traces of blood-stained fluid in the pericardium and pleural cavities, evidently no more than a little oozing through the tissues, with no external rupture and no question of cardiac tamponade. The greater parts of both kidneys were normal. One area of partial infarction was found on the kidney where the tubules were infarcted, but the glomeruli appeared entirely normal. That is a condition that is sometimes seen when a critical level of oxygen deficit is met with. The kidney tubules are more sensitive to anoxemia than the glomeruli, and hence it is possible to get differential necrosis of tubules without glomerular changes. I think the anuria was due to the state of shock and diminished blood pressure.

DR. BLAND: Was the brain examined?

DR. MALLORY: No.

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established in 1828

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND  
PUBLISHED UNDER THE JURISDICTION OF THE  
COMMITTEE ON PUBLICATIONS

Official Organ of

THE MASSACHUSETTS MEDICAL SOCIETY  
and

THE NEW HAMPSHIRE MEDICAL SOCIETY

## EDITORIAL BOARD

Joseph Garland, M.D.  
William B. Breed, M.D.  
George R. Minot, M.D.  
Frank H. Lahey, M.D.  
Shields Warren, M.D.  
George L. Tobey, Jr., M.D.  
C. Guy Lane, M.D.  
William A. Rogers, M.D.

Stephen Rushmore, M.D.  
Henry R. Viets, M.D.  
Robert M. Green, M.D.  
Charles C. Lund, M.D.  
John F. Fulton, M.D.  
A. Warren Stearns, M.D.  
Dwight O'Hara, M.D.  
Chester S. Keefer, M.D.

## ASSOCIATE EDITORS

Thomas H. Lanman, M.D. Donald Munro, M.D.  
Henry Jackson, Jr., M.D.

Walter P. Bowers, M.D., EDITOR EMERITUS  
Robert N. Nye, M.D., MANAGING EDITOR  
Clara D. Davies, ASSISTANT EDITOR

SUBSCRIPTION TERMS: \$6.00 per year in advance, postage paid, for the United States (medical students, \$3.50 per year); Canada, \$7.04 per year, Boston funds; \$8.52 per year for all foreign countries belonging to the Postal Union.

MATERIAL for early publication should be received not later than noon on Friday.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston, Massachusetts.

## PROCUREMENT AND ASSIGNMENT SERVICE

Every physician should read the communication from Major Sam F. Seeley, director of the Procurement and Assignment Service, which appeared in the May 2 issue of the *Journal of the American Medical Association*. Every physician should return his enrollment blank promptly. The demand for doctors in the Army is still great. At least 10,000 more will be needed by the end of the year. The Navy will also require more physicians, although its need is not so great as that of the Army.

Heretofore, there has been considerable delay in answering applications for commis-

sions in the Medical Corps of the United States Army. This delay and the resulting uncertainty have undoubtedly deterred many physicians from applying for commissions. To overcome this, the Army has adopted a new method.

Beginning about May 15, recruitment boards consisting of a medical-corps officer and a line officer will be sent into each state east of the Mississippi. These boards will work in co-operation with the state chairmen of the Procurement and Assignment Service, securing from them the names of physicians, and will then communicate with these men, initiate the applications and physical examinations, make final decisions, and administer the oath of office immediately. By this method, a physician can be assigned to duty within fourteen days of the time he applies and is examined.

For the most part, commissions will be given in the grade of first lieutenant. The great need of the Army at present is for battalion and regimental surgeons for service with troops. Applications for commissions for captain may be granted between the ages of thirty-seven and forty-five. Above that age, commissions will not be granted except in rare instances and for a special need. No commissions will be given by these boards for affiliated units.

The Navy will send a medical officer from the First Naval District to co-operate with the state chairmen of Maine, New Hampshire, Massachusetts, Vermont and Rhode Island, to perform a similar service.

Physicians will not be commissioned in either the Army or the Navy unless they are cleared as available by the Procurement and Assignment Service.

The Army and the Navy are doing their utmost to cut red tape and make it as easy as possible for physicians to receive commissions. Physicians of the First Corps Area and Naval District should set an example to the rest of the Nation by their willingness and promptness to respond to this call. The need is great; the response must be prompt.

## ALCOHOLISM: A MEDICAL AND COMMUNITY PROBLEM

Of the three greatest public-health problems in the United States,—tuberculosis, syphilis and alcoholism,—only alcoholism has not yet been completely accepted as a medical problem. It is in endemic condition, however, and its prevalence can be estimated when one recalls that only a small proportion of those who drink to excess are diagnosed and are receiving treatment.

Alcoholism is difficult to define, but it is generally agreed that a person who uses alcohol to the extent of being unable to maintain his position in a family, occupational or community group is to be considered an alcoholic; such a person presents a medical and, particularly, a psychiatric problem. The moral aspects of drinking are no longer emphasized, but because of the physical and mental damage inevitably resulting from prolonged drinking, alcoholism must be considered a public-health problem and handled with the technics of preventive medicine.

Acute and chronic alcoholism result in part from personal psychologic inadequacy. Thus, in addition to individual tolerance and habituation, personal factors determine largely why some persons can drink a given volume of alcohol in a given period and suffer no untoward effects, whereas others, under the same conditions, demonstrate abnormal behavior. These variations appear to be conditioned principally by personal experience and may be molded by the forces to which the person has been exposed as a child and as an adolescent. The difficulties encountered before the onset of alcoholism may be precipitating factors rather than actual causes.

Generalizations about the causes of acute and chronic alcoholism are inconclusive, but the person who is unwilling or unable to face the realities of life frequently becomes an alcoholic. Such a person tends to substitute for mature reactions the infantile regressive patterns that in childhood were expressed in temper tantrums, too prolonged bedwetting and other neurotic traits. One of the

commonest forms of neurotic behavior is drinking to excess.

Prolonged drinking usually results in some form of neuropsychiatric disorder that is often not recognized. It may be an avitaminosis, such as alcoholic polyneuritis or pellagra caused by faulty dietary habits. Delirium tremens may develop, or there may be a frank alcoholic psychosis, such as Korsakow's syndrome. Between 1915 and 1935, 6 per cent of the cases of alcoholism admitted to the Boston City Hospital were diagnosed as delirium tremens. About 60 per cent of all patients admitted to Massachusetts mental hospitals in the last twenty-five years gave a history of excessive drinking.

The cost of hospital care of alcoholics is large, especially since most of them are cared for without charge in institutions supported by states or cities. The maintenance of courts for the penal disposition of inebriates and the expense of maintaining alcoholic addicts in state penal institutions and the county houses of correction increase this cost. In addition the relief care of their families and dependents, whose income and earning power have been lost, necessitates large local or state appropriations every year.

There are very few places in Massachusetts where alcoholics are welcomed for treatment unless they can afford the high costs of private institutions. They are not wanted at general hospitals, for the most part, and if received at all, are cared for only during the acute phases of their condition or sent in presumably for observation or study. They are not accepted at state mental institutions unless they are suffering from alcoholic psychoses or equally severe mental illnesses in which alcoholism plays a part. Few private physicians are equipped by training to treat alcoholic patients, and private psychiatrists are reluctant to accept them, for they are usually not co-operative or are resistant to treatment. There are a few small hospitals, such as the Washingtonian Hospital in Boston, where they can receive therapy.

In the treatment of acute or chronic alcoholism, when the patient's physical condition has been

improved by rest, the administration of sedative and analgesic drugs to relieve nervous tension, the restoration of fluids, dietary readjustment and such specific measures as are appropriate, psychotherapy should be attempted. The first requisite is that the patient express a desire to overcome the habit and agree to co-operate with the therapist. Complete abstinence from alcoholic beverages is an absolute necessity. The aim of psychotherapy is to review the past history, to bring into focus the factors that have built up the drinking habit, and to help the patient to reorganize his life on the basis of total abstinence from drinking. Boredom and social inadequacy, which often play a large part in the temptation to drink, can be partially remedied with thought and planning.

In Massachusetts, facilities for treating indigent alcoholic patients are sorely needed, and should be made available through clinics and in general hospitals. Clinics operated with the aim of preventing secondary neurologic and psychiatric complications should be established in connection with the institutions at present administered by the Department of Mental Health. These clinics cannot be established without a concurrent educational program, in which federal, state and local authorities should participate. This program might be similar to the one that has been so effective in directing attention to syphilis as a public-health problem. The clergy, the press and progressive physicians can be very effective in promoting co-operation between alcoholic patients and the organizations that can aid them.

## IN MEMORIAM

### NORMAN PAUL HERSAM

1884—1942

Norman Paul Hersam was born in Stoneham fifty-seven years ago. He graduated from the Stoneham High School, the University of California and Harvard Medical School. He interned at the Providence City Hospital and took post-graduate work in plastic surgery at the Massachusetts General Hospital. He then practiced medicine in his own town until his death, living on the street named after his grandfather.

Dr. Hersam was school physician in Stoneham for over twenty years, and at the time of his death he was a censor in the Middlesex East District Medical Society. He was a fellow of the American Medical Association and was on the staffs of the Choate Memorial Hospital in Woburn and the Winchester Hospital.

Dr. Hersam had many hobbies. He loved fine music and had the skill of a concert pianist. He was an artist of great talent, and his home is adorned by many of his paintings. His skill as a woodcraft was widely known; he carved many objects and made many violins that were noted for their beautiful tones. To know Dr. Hersam intimately was to cherish a friendship everlasting.

BE IT RESOLVED: That the members of the Middlesex East District Medical Society by his death on January 15, 1942, have lost a beloved and respected associate and one who at all times carried the highest standard of ethics and clean living; and

BE IT FURTHER RESOLVED: That a copy of these resolutions be spread upon the records of the society and that the secretary be directed to send a copy to his wife, Mrs. Maybelle Jane Hersam and to the *New England Journal of Medicine*.

JOSEPH H. KERRIGAN, M.I.  
RICHARD W. SHEEHY, M.I.

## MEDICAL EPONYM

### PAGET'S DISEASE (OSTEITIS DEFORMANS)

Sir James Paget (1814-1899), Bart., D.C.L., LL.D., F.R.S., consulting surgeon to St. Bartholomew's Hospital, read a paper "On a Form of Chronic Inflammation of Bones (Osteitis Deformans)" in 1876 before the Royal Medical and Chirurgical Society of London. It appears in the *Medico-Chirurgical Transactions* (42:37-63, London, 1877). A portion of the text follows:

The disease affects most frequently the long bones of the lower extremities and the skull, and is usually symmetrical. The bones enlarge and soften, and those bearing weight yield and become unnaturally curved and misshapen. The spine, whether by yielding to the weight of the overgrown skull, or by change in its own structures, may sink and seem to shorten with greatly increased dorsal and lumbar curves; the pelvis may become wide; the necks of the femora may become nearly horizontal, but the limbs, however misshapen, remain strong and fit to support the trunk.

In its earlier periods, and sometimes through all its course, the disease is attended with pains in the affected bones, pains widely various in severity and variously described as *rheumatic*, *gouty*, or *neuralgic*, not especially nocturnal or periodical. It is not attended

with fever. No characteristic conditions of urine or faeces have been found in it. It is not associated with syphilis or any other known constitutional disease, unless it be cancer.

In three out of the five well-marked cases that I have seen or read of cancer appeared late in life; a remarkable proportion, possibly not more than might have occurred in accidental coincidences, yet suggesting careful inquiry.

R. W. B.

## MASSACHUSETTS MEDICAL SOCIETY

### OFFICE OF THE SECRETARY

The following letter, which should be of interest to all members of the Massachusetts Medical Society, was recently received from J. W. Holloway, Jr., director of the Bureau of Legal Medicine and Legislation of the American Medical Association.

MICHAEL A. TIGHE, *Secretary*

\* \* \*

TO THE SECRETARIES OF THE STATE MEDICAL ASSOCIATIONS:—  
The Senate Committee on Military Affairs has reported H. R. 4476 to the Senate with the recommendation that it pass.

The first section of the bill, as reported, reads, in part.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled, That the Secretary of War be, and hereby is, authorized out of any moneys available for the War Department . . . to provide for the employment of interns who are graduates of or have successfully completed at least four years' professional training in reputable schools of medicine or osteopathy in the Medical Department, at not to exceed \$720 per annum.

This authorization will represent permanent legislation. It does not make it mandatory that the War Department select interns from osteopathic schools and if the present high standards are maintained in the Medical Department, no such appointments will be made. The authorization, however, does constitute to a certain extent a Congressional viewpoint that osteopaths will construe as a recognition of their competency to serve in the Medical Corps of the Army. This implication will be pointed out by the osteopaths not only in connection with any future Congressional demands they make but also in connection with state legislation that they may sponsor.

For the foregoing reasons, it is important that state medical associations urge their senators to eliminate so much of the authorization from the bill as is underscored. If the underscored language be eliminated, the War Department will still be authorized to employ interns and may exercise full discretion in their selection.

Sincerely yours,

J. W. HOLLOWAY, JR.

## COMMITTEE ON MATERNAL WELFARE

### CASE HISTORY: FATAL DIABETES IN PREGNANCY

A thirty-year-old multipara who was seven months pregnant arrived at the hospital in active labor and in diabetic coma. Two previous pregnancies had been normal, with living children, and a third had resulted in a stillbirth. The patient was known to have had diabetes for four years; during this particular pregnancy, however, she had had no prenatal care, nor had she seen a physician for her diabetes. Besides the diabetes, the pregnancy was complicated by an "inflammation of the right leg," which may or may not have been a phlebitis. The patient arrived at the hospital at 3:45 a.m. Five minutes later, she delivered herself of a stillborn infant, and in spite of insulin and intravenous glucose to combat the coma, she did not regain consciousness and died about twenty hours after delivery.

*Comment.* It is unfortunate that details of the history are entirely lacking, but it is very evident that the pregnancy aggravated the diabetes, which was the direct cause of death. The modern treatment of diabetes in pregnancy requires very constant medical supervision. Patients with mild diabetes are unstable during pregnancy; those with severe diabetes are extremely unstable. Labor at seven months with a stillborn infant is not at all infrequent in diabetic patients, even those under excellent medical care.

Patients with diabetes may begin a pregnancy with perfect confidence so far as their own survival goes; not so with the babies. Modern treatment has decreased the infant mortality in diabetic mothers very materially, but miscarriages, premature labors and dead babies do occur, and occasionally patients go to term and deliver themselves of stillborn infants.

The death in the case presented is attributable solely to the patient herself, who consulted no physician during her pregnancy. Had she been under good medical care, that is, under specialized diabetic care, she certainly would not have lost her life, and it is very possible that the baby would have survived.

### DEATHS

HIGGINS—JAMES H. HIGGINS, M.D., of Marston's Mills, died April 7. He was in his seventy-second year.

Born in Marshfield, Missouri, Dr. Higgins received his degree from the College of Physicians and Surgeons, Boston, in 1894. He was formerly town and school physician for the town of Barnstable, and a member and chairman of the Barnstable Board of Health. He was a former president and secretary of the Barnstable District Medical Society, and a fellow of the Massachusetts Medical Society and the American Medical Association.

His widow, two sons and three daughters survive him.

**RODRICK** — ALBERT F. RODRICK, M.D., of Beverly, died April 30. He was in his seventieth year.

Dr. Rodrick received his degree from Tufts College Medical School in 1901. He was a former member of the Massachusetts Medical Society and the American Medical Association.

He is survived by two sons and two sisters.

**SISE** — LINCOLN F. SISE, M.D., of Brookline, died April 28. He was in his sixty-eighth year.

Born in Medford, Dr. Sise received his degree from Harvard Medical School in 1901. He was visiting anesthetist of the Boston City and Long Island hospitals, clinical assistant in anesthesia at Harvard Medical School and lecturer on anesthesia at Tufts College Medical School, and for many years, preceding his retirement three years ago, was the chief anesthetist at the Lahey Clinic. He was a member of the American Society of Anesthetists, and a fellow of the Massachusetts Medical Society and the American Medical Association.

He is survived by his widow, two sons and three grandchildren.

**SWIFT** — WALTER B. SWIFT, M.D., of Boston, died May 2. He was in his seventy-fifth year.

Born in Geneva, Switzerland, Dr. Swift received his degree from Harvard Medical School in 1907. Dr. Swift specialized in the treatment of nervous diseases, particularly speech defects. He was formerly associated with the Boston City Hospital, Tufts College Medical School and the Boston State Hospital. He was a fellow of the Massachusetts Medical Society and the American Medical Association.

He is survived by his widow and two daughters.

**WATSON** — FRANCIS S. WATSON, M.D., of South Dartmouth, died May 5. He was in his eighty-ninth year.

Born in Milton, Dr. Watson received his degree from Harvard Medical School in 1879. After an internship at the Massachusetts General Hospital, he studied abroad and then began the practice of surgery in Boston. During his career, he was associated with the staffs of the Boston City, Children's and Carney hospitals and the Boston Dispensary, having been surgeon-in-chief at the Boston City Hospital from 1906 to 1910. Specializing in genitourinary surgery, Dr. Watson was, for many years, in charge of this department at the Harvard Medical School and at one time was president of the American Association of Genito-Urinary Surgeons. He was honorary president of the International Urological Society, and was a member of the Massachusetts Medical Society and the American Medical Association.

His widow survives him.

## WAR ACTIVITIES

### CIVILIAN DEFENSE

#### STATE HOSPITAL OFFICER

Appointment of a state hospital officer as an official of Emergency Medical Service has been recommended by the Medical Division of the United States Office of Civilian Defense for densely populated states in the target areas. These areas are principally in the First, Second, Third, Fourth, Eighth and Ninth defense regions.

The principal function of the hospital officer will be the planning of emergency base hospitals for the reception of

civilian casualties and other hospital evacuees. An official memorandum sets forth his duties as follows:

1. To survey the hospitals throughout the state (excluding those in the exposed cities), to determine how many beds can be put into immediate use in emergency with existing kitchen, laundry, sanitation and other engineering facilities
  - (a) By clearing patients to their homes.
  - (b) By restricting admissions.
  - (c) By use of rooms not normally used for patients.
  - (d) By rehousing medical and nursing staff and other hospital personnel outside the hospital.
  - (e) By use of neighboring buildings (schools, hotels and so forth) for patients (or staff).
  - (f) By extra bed accommodation in temporary structures erected on available grounds adjacent to the hospital.
2. To assist in designating, for each casualty hospital or group of hospitals in each exposed city,
  - (a) The line of evacuation to the base.
  - (b) The transport arrangements.
  - (c) The emergency base hospitals provisionally allotted to each casualty unit.
3. To keep constantly informed of the bed state of every hospital in his area by weekly returns.
4. To advise the Office of Civilian Defense, through the regional medical officer, on the need for providing additional accommodations, for example, by temporary construction or by converting convalescent homes, hotels, school dormitories or other structures into hospitals.
5. To report to the regional medical officer of the Office of Civilian Defense any exceptional condition requiring action (for example, matters beyond state boundaries, or required by the needs of the military situation) and to forward to him copies of a monthly summary report on the state's emergency hospital program. Where a hospital outside a state boundary is readily accessible for the reception of casualties from an exposed city, this fact should also be noted.
6. To maintain constant touch with the other service departments of the state defense council (for example, evacuation and so forth).
7. To supervise the distribution of medical and hospital supplies under the direction of the state civilian defense property officer and report any threatened deficiency to the regional medical officer.
8. To supervise staff arrangements for emergency base hospitals and for reception areas.
9. To control movements of medical and nursing staff, as well as of casualties, in any situation affecting emergency base hospitals.

The hospital officer must work in close collaboration with the state evacuation authority, the memorandum points out. In addition, he may find it necessary to collaborate with the state officer in charge of institutions for the care of mental patients, if such hospitals are to be used as emergency base hospitals for the reception of casualties and other patients evacuated from urban hospitals. Transport arrangements are to be handled in collaboration with the evacuation authorities of the state and the military authorities of the area.

# MISCELLANY

## MEDICAL AND SURGICAL RELIEF COMMITTEE OF AMERICA

The Medical and Surgical Relief Committee of America will distribute literature concerning its nation wide activities and sell its official emblem at the forthcoming convention of the Massachusetts Medical Society on May 26 and 27

Since America entered the war, the committee has been furnishing medical and surgical supplies to emergency field stations, needy hospitals and other recognized relief agencies throughout the country. One hundred and forty four emergency medical field sets have been supplied to defense officials in potential target areas in twenty five states of these, Massachusetts has so far received fourteen

The following Boston physicians are affiliated with the committee: Dr John D Adams, Dr Fuller Albright, Dr Arthur W Allen, Dr Bennett F Avery, Dr Ralph S Banay, Dr P F Butler, Dr Richard B Cattell, Dr Sara M Jordan, Dr Frank H Lahey, Dr C H Lawrence, Dr Ralph D Leonard, Dr Philip E Meltzer, Dr Vals Menkin, Dr Harris P Mosher, Dr Abraham Myerson and Dr Paul Dudley White. Other Massachusetts physicians in field: Dr Hilbert T Day, of Cambridge, and Dr Francis W Palfrey, of South Duxbury

## RÉSUMÉ OF COMMUNICABLE DISEASES IN MASSACHUSETTS FOR MARCH, 1942

DISEASES	MARCH 1942	MARCH 1941	FIVE YEAR AVERAGE*
Anthrax or polio myelitis	0	1	0
Cholera	194	1408	1492
Diphtheria	16	8	12
Dog bites	870	655	763
Dysentery bacillary	0	3	101
German measles	1184	147	388
Gonorrhea	323	324	2787
Measles	3747	3127	12
Meningitis meningo-coccal	27	10	1101
Meningitis other forms	25	3	5
Mumps	291	1349	665
Paratyphoid infections	0	3	1010
Pneumonia lobar	517	369	534
Scarlet fever	1474	467	281
Syphilis	443	285	32
Tuberculosis pulmonary	285	27	4
Tuberculosis other forms	17	2	6
Typhoid fever	2	2	1034
Undulant fever	2	6	
Whooping cough	1007	969	

\*Based on figures for preceding five years

## GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Anthrax was reported from Boston, 1, Haverhill, 2, total, 3  
Diphtheria was reported from Adams, 1, Boston, 2, Fall River, 2, Lowell, 2, Medford, 1, Somerville, 2, Springfield, 2, West Brookfield, 1, Wrentham, 3, total, 16  
Encephalitis, infectious, was reported from Belmont, 1, Boston, 1, Pittsfield, 1, total, 3  
Meningitis, meningococcal, was reported from Ashby, 1, Boston, 6, Brookline, 2, Cambridge, 1, Camp Edwards, 1, Canton, 1, Chelsea, 3, Fall River, 1, Lowell, 1, Marlboro, 1, Melrose, 1, Milford, 1, North Adams, 1, Springfield, 2, Quincy, 1, Worcester, 3, total, 27  
Meningitis, other forms, was reported from Boston, 1, Brockton, 3, Cambridge, 1, Canton, 1, East Bridgewater, 1, Gloucester, 1, Hampden, 1, Holyoke, 2, Lawrence, 1, Lexington, 1, Lowell, 1, Medfield, 1, Needham, 1, Northampton, 1, Quincy, 1, Revere, 2, Salem, 1, Somerville, 1, Springfield, 1, Watertown, 1, Wellesley, 1, total, 25  
Septic sore throat was reported from Boston, 12 Brock-

ton, 1, Cambridge, 3, Marlboro, 1, Medford, 2, Merrimac, 1, Millbury, 1, Newburyport, 2, Northampton, 2, Quincy, 1, Stoughton, 1, Waltham, 1, Worcester, 3, total, 31  
Tetanus was reported from Haverhill, 1, total, 1  
Trichinosis was reported from Boston, 2, Wakefield, 1, total, 3

Typhoid fever was reported from Boston, 2, total, 2  
Undulant fever was reported from Greenfield, 1, Uxbridge, 1, total, 2

Typhoid fever and tuberculosis, other forms, struck record low incidences this month

Anterior poliomyelitis, bacillary dysentery, paratyphoid fever, undulant fever, whooping cough and lobar pneumonia were reported at figures below the five year averages

Dog bites reached a record high figure this month  
Mumps, following a months drop from record figures, is again reported at record high incidence

Chicken pox, diphtheria, German measles, meningococcal meningitis, scarlet fever and pulmonary tuberculosis were reported at figures above their five year averages

Cases of animal rabies were reported in Tewksbury and Burlington, maintaining the focus in the northern section of the State (Middlesex County)

## VICE-PRESIDENT OF PHARMACEUTICAL FIRM DIES

Malcolm Galbraith, vice president and director of sales of the Upjohn Company, died April 10 in Kansas City. Mr Galbraith was born in Bowmanville, Ontario, Canada, October 23, 1876. He received his bachelor of pharmacy degree at Ontario College of Pharmacy in 1898, entering the drug business in Ontario the same year. He later became a naturalized citizen of the United States. In 1909, he left the H. K. Mulford Company, of Philadelphia, to join the Upjohn Company. In October, 1929, he was elected to the board of directors and named director of sales. He was made vice president of the company in May, 1936

## NOTES

Four promotions at the Harvard Medical School, effective July 1, were recently announced. Dr John H Mueller, associate professor of bacteriology and immunology, has been named professor of bacteriology and immunology, he will take charge of the department at the Medical School and also at the School of Public Health.

The following men were named to associate professorships: Dr Fuller Albright, now assistant professor of medicine, Dr Allan M Butler, now assistant professor of pediatrics, and Dr Hiram H Merritt, now assistant professor of neurology. In addition, Dr Frederick J Stare has been appointed assistant professor of nutrition effective July 1

Dr William Dameshek, assistant professor of medicine at Tufts College Medical School, was recently appointed professor of clinical medicine.

The Committee on Faculty of Middlesex University recently announced the appointment of two new full time teachers to the faculty of the School of Medicine, for the school year starting July 1, 1942. Dr Fritz Schweinburg has been appointed professor of bacteriology. Born in Vienna, Dr Schweinburg received his medical degree from the University of Vienna in 1908, served as assistant pathologist under Professor Sternberg till 1910 and as temporary head of the Department of Medicine at the Rudolfs hospital in Vienna until 1916. During World War I,



he served in the Austrian army as head of an epidemic hospital, and then became a member of the staff of the Pasteur Institute of Vienna and head of that institution from 1934 to 1938. Dr. Peter Gruenwald has been made assistant professor of histology and embryology. Born in Bohemia, Dr. Gruenwald received his medical degree from the University of Vienna in 1936, and was associated with the histological department of the university until he came to the United States in 1938.

## CORRESPONDENCE

### PROTECTION FOR PHYSICIANS IN THE ARMED FORCES

The following sentences made the last two paragraphs of my presidential report read at the annual meeting of the Middlesex South District Medical Society on April 22, 1942, and I hope that the ideas contained in them may help others:

Your officers are very much aware of the fact that this is a war year and that many of our fellows are young and in good health and so are privileged to serve their country conspicuously, as we all should be glad to do. We wondered if some kind of round robin pledge to those in service could be sent from us who remain at home concerning our attitude in regard to the patients of those who go, but after talking with many members of our society, we decided against such action. We can assure those who go that it is the general desire that they will find loyal patients and consultants when they return to civil life. We believe that this will best be accomplished if those who go into the service make definite arrangements for the referral of patients from their homes or offices to a doctor or group they trust so that their patients will be cared for in an approved way and returned to them on their return to practice.

Finally, it is the hope and desire of your officers that if during the war any crisis, financial or otherwise, arises in the family of the doctors who serve away from home, that the family will let the president of this *their* medical Society know promptly, for your officers know ways of helping and pledge themselves to investigate and help quickly. Later I hope to write this desire of ours to each one individually.

HILBERT F. DAY, *President*  
Middlesex South District Medical Society

412 Beacon Street  
Boston

### "AMERICAN INSTITUTE FOR PSYCHOANALYSIS"

*To the Editor:* In an editorial entitled, "American Institute for Psychoanalysis," published in the April 16, 1942, issue of the *Journal*, several statements are made which we feel ought to be answered. The editorial refers to the fact that a group of members and students of the New York Psychoanalytic Society and Institute resigned within the last year as a protest against what they termed "dogmatism in psychoanalytic education" and established an Association for the Advancement of Psychoanalysis and an American Institute for Psychoanalysis. At the same time, they emphasized the difference between what they termed "classical" and "non-classical" training in psychoanalytic theory and practice.

In reply to the announcement of this group, the New York Psychoanalytic Society and Institute emphasized,

among other things, that its records showed "differences in theoretical and technical viewpoints were the issue which led to these resignations," but "they curved only because, within the Institute as a whole, dissident group violated academic freedom by attempting to maintain an exclusive influence on the education of a small group of students" and "this could not be permitted."

In the editorial, it is stated that "a justifiable criticism of some psychoanalysts of the Freudian school or of some of the psychoanalytic societies is that they insist on orthodoxy, the incontrovertible correctness of Freud's fundamental concepts." We would like to emphasize that such a statement is not borne out by what we know of the scientific and historical development of psychoanalysis.

Freud's work cannot be understood unless its progress is followed through his various publications, thus obtaining a coherent picture, as in all the fundamental sciences of the evolution of psychoanalysis from its early beginnings. The alleged changes in psychoanalysis, as emphasized by its opponents, have not overthrown the original concepts and discoveries, for what has taken place is essentially a new development or viewpoint as fresh theories are explored through accumulating clinical experiences.

A few statements will help to clarify our attitude. For instance, an editorial preface to the English translation of Freud's *Collected Papers* states: ". . . his [Freud's] path lay through a jungle hitherto completely unexplored. Rarely did his path follow a straight line for long; deviations, detours, fresh departures were often necessary, and occasionally even the retracing of his steps." One of Freud's most important modifications concerned his changed attitude on the importance of sexual traumas in childhood, since he discovered that it was not necessary for them to be actual experiences, but might be in many instances related only to the fantasies of the individual. In a paper published in 1905, entitled "My Views on the Part Played by Sexuality in the Aetiology of the Neuroses," he emphasized that, as a result of more extensive clinical experience, he was able to correct the most momentous of his early errors, thus necessitating a change in the conception of the mechanisms of hysterical symptoms.

Furthermore, in Freud's revision of the anxiety problem in 1926, which is so important for an understanding of the neuroses, he again showed that he was not an entrenched advocate of scientific dogmatism. For instance, he states, "Anxiety causes the repression, and not, as I earlier stated, the repression the anxiety." In his *Autobiography*, too, he writes, "The science of psychoanalysis is seldom able to deal with a problem completely, but it seems destined to give valuable contributory help in a large number of regions of knowledge."

These changing viewpoints of Freud, in both theory and technique, took place under the pressure of widening and deepening experience, and the attitudes of both Freud and the psychoanalysts of the Freudian school are free from dogmatism and show a willingness to change theories in the light of broadening knowledge. Many of these analysts have introduced new techniques as modifications of the original basic theories.

The viewpoints of this dissident group do not appear to us as revolutionary as many uninformed persons might be led to believe; consequently, their insistence on the dogmatism of the so-called orthodox Freudians will not bear critical investigation.

We should also like to draw your attention to an editorial in the September 21, 1939, issue of the *Journal*, en-

itled 'The Organization and Development of the Psychoanalytic Association,' on the occasion of the publication of the *Bulletin of the American Psychoanalytic Association*, which states in part: "It shortly became evident that meticulous training in psychoanalysis was essential to an adequate understanding of this method of treatment. In view of this, the association gradually altered its structure to become a federation of local psychoanalytic societies, each local society admitting only physicians with adequate training."

The American Psychoanalytic Association has set a high standard of organization. Through the local societies it exerts a wide influence. It is to be congratulated not only on the standards it has set but also on the care that has been used in selecting members. The first number of its bulletin, giving the details of the organization, is a valuable historical document.

We can only hope that the American Psychoanalytic Association will continue with its high standards in the selection and training of its members. Perhaps the organization of a secessionist group is in itself a proof of how high the standards actually are.

ISADOR H. CORIAT, MD, *President*  
Boston Psychoanalytic Society

M. RAIPH KAUFMAN, MD, *Chairman*  
Educational Committee, Boston Psychoanalytic Institute

## REPORT OF MEETING

### GREATER BOSTON MEDICAL SOCIETY

A regular meeting of the Greater Boston Medical Society was held at the Beth Israel Hospital on January 6. Dr Samuel Gargill presiding. Dr Alan I. Guttmacher, of Johns Hopkins University School of Medicine, discussed 'Spontaneous Abortions and Malformed Children. What can be done about them?'

The speaker first considered causes of abortions and what may be done to decrease the incidence. The amount of physical exertion allowed by physicians is variable but Dr Guttmacher permits any activity in which the patient is accustomed. The only restriction is long automobile rides during the first sixteen weeks, such trips by other methods are not forbidden. This too, which is admittedly a throwback to the days of automobiles and rough roads, probably has no real basis in the present era. An inherent germ plasm defect is the most commonly recognized cause of abortions of the spontaneous variety. Here there is nothing to save. There may be an abnormal embryo or phoblast or both, or any degree of the combination of spontaneous abortions from this cause have been roughly estimated from 75 to 85 per cent.

The course of most abortions is fairly constant. There is a normal growth for several weeks before the fetus is to develop, then it dies, and is passed several weeks later. The last episode probably takes place about six weeks after death, which means that the pathologic ovum is but a relatively short time. Abortions in normal species usually occur later. Failure to be fertilized or to develop normally is common to all mammalian ova. It has been estimated that in monkeys there are 24 per cent more corpora lutea than embryos and that there is a 1 per cent loss in the opossum. Usually a germ plasm defect causes this failure of fertilization. Possible causes suggested by analogy include defective genes or chromosomes, or both for it is known that all mammals have defective genes but that the results are apparent

only if sperm and ovum have the same defect, faulty intrauterine mechanism, for many factors are essential to the implantation of the ovum and the setting up of adequate nutrition, and improper intrauterine environment in the form of oxygen, hormones and vitamins. The causes of abortion in nonpathologic ova are also multiple placental abnormalities, such as complete placenta membranacea, placenta previa and premature separation, maternal diseases, especially of the toxic variety, but these and tuberculosis and syphilis are likelier to cause premature labor, endocrine dyscrasias, especially a lack of progesterone, laparotomies, especially if a pelvic operation is undertaken, and here the use of heavy sedation, with morphine and large amounts of progesterone, is helpful defects of the regenerative organs, but such conditions are apter to cause sterility than abortions, and the role of fibroids is certainly overrated, and psychic and physical trauma, which are usually not serious if the fetus is healthy, but may hurry an inevitable event or may be a coincidence.

It becomes apparent that the proper treatment of threatened or incipient abortions should be based on a knowledge of whether an ovum is healthy or diseased. Such facts, however, are not easily obtainable. Dr Rutherford, at the Boston Lying in Hospital, has made suction biopsies of bleeding patients and found that if necrotic deciduum is obtained abortion cannot be prevented by any means, whereas there is a 50 per cent chance of survival on expectant treatment if the biopsy is normal. Bleeding is considered an important symptom, but it was not until recently that it was learned that 21 per cent of normal pregnant women stain during the first twenty eight weeks. There was no characteristic difference in the bleeding, except that the passing of clots and the presence of uterine cramps were noted in only one of those who did not abort, whereas these findings were common in those who aborted. Vomiting may prove a valuable prognostic aid, for those who eventually aborted had only half the nausea and vomiting experienced by the control patients. Hormonal studies on prolactin and pregnandiol levels are of no importance unless there is a consistently negative Friedman test and repeated quantitative determinations are made. The constantly increasing size of the uterus is a good sign, whereas a decrease in the size of the breasts and a loss of weight in the presence of a good appetite after the fourth month are bad omens.

Treatment varies with the symptoms. For staining, rest and abstinence from coitus for two weeks are advised. With frank bleeding bed rest is demanded as well as vitamin E and progesterone. Examination for a local cause is carried out after one week, and it is usually possible after ten days to predict the outcome. The absence of nausea and vomiting is considered an unfavorable sign, and no treatment is given except advice unless the patient demands it. The onset of cramps requires immediate hospitalization for the event is then about twenty four hours away. If the cervical os is open, immediate dilatation and curettage are carried out. All products should be saved at all costs, both to determine the totality of the abortion and to evaluate the viability of the fetus, so that advice may be given for future pregnancies. If the ovum is abnormal, a new attempt at conception is suggested in two weeks. Thyroid extract is administered for a few weeks if the basal metabolic rate is depressed, for this may stimulate the hormonal system and foster better intrauterine conditions. If the ovum is normal the patient should be thoroughly examined and put in the best possible condition. It is then advised that conception should

not be attempted for a six-month interval, to allow for a correction of the unknown cause. The condition of the husband is considered of little importance.

Abortions should not be considered habitual unless there are more than three successive ones, because any less than that number may be merely on the law of averages or from random causes. There is a high incidence of spontaneous cures among the cases with random causes, which comprise by far the largest group. Less than 1 per cent of cases occur in women who have had more than three abortions. And in this group, there are few if any tested cures. In the treatment of threatened abortion in suspected patients, bed rest is vital. In addition, the administration of progesterone may be started four weeks before the time of the anticipated abortion and continued until four weeks from term. Antuitrin may be employed in the hope of perpetuating the existing corpus luteum.

Congenital malformations seem to be related to germ-plasm abortions and sterility, for they are all considered evidence of regenerative inefficiency. These malformations often follow a long period of sterility or a recent abortion. Furthermore, there is a high incidence of abnormal offspring in pregnancies in which threatened abortion has been treated with progesterone. The wisdom of such therapy is therefore again questioned.

The discussion was opened by Dr. Harold Rosenfield, who is still very cautious in the prenatal restriction of his patients because of the danger of criticism in the event of an abortion. When staining occurs, he advises complete bed rest until two days have passed without any show and carries out other measures, such as the administration of hormones and wheat-germ oil. In the prophylaxis of abortions, he has found that 35 per cent may be attributed to defective sperm, and he studies the husband, especially from the standpoint of fatigue.

Dr. Arthur Hertig, in discussing habitual abortions, stated that this is apparently not a different group, for there is the same variety of causes as in any group. But any given habitual aborter is prone to repeat the same complex. He has never seen an abortion caused by trauma. The causes of abortion are 70 per cent fetal, 46 per cent being accounted for by true "blighted ova." A study of embryos as early as the eleventh day of gestation indicates that about 50 per cent of all ova are pathologic, so that many blighted ova may merely pass out with the next menstrual period, which may be slightly late and profuse. Bleeding at the time of implantation may simulate the first missed period and confuse calculations.

Dr. Robert Rutherford stressed the effect of circumvallate placenta in the production of abortion; this is the commonest cause of midtrimester miscarriage. Progesterone is of no therapeutic value. Intense therapy with this hormone may serve to keep a pathologic ovum in the uterus for the entire nine months, with the real danger of degeneration into a hydatidiform mole. Such patients may even retain the products of conception after a therapeutic dilatation and curettage, and thus fail to resume the normal cycle.

Dr. Saul Berman suggested that some male factor is responsible in early 70 per cent of the cases. He raised the question whether vitamin E is carcinogenic. He considers the study of the husband and of the thyroid gland to be essential in cases of habitual abortion.

In conclusion, Dr. Guttmacher stated that although the male factor may be a cause in well over 50 per cent of cases of sterility, he does not believe it to be of significance in germ-plasm abortions.

## BOOK REVIEWS

*Abdominal Surgery of Infancy and Childhood.* By William E. Ladd, M.D., and Robert E. Gross, M.D. 4°, cloth, 455 pp., with 268 illustrations and 39 tables. Philadelphia: W. B. Saunders Company, 1941. \$10.00.

This book gives the record of an era in surgery. During the last twenty-five years, pediatricians and surgeons have co-operated to reduce the mortality in many diseases of infancy and childhood that can be cured by surgery. The results are given here in actual figures and are achievement of first magnitude. The book is a masterpiece of orderliness and simplicity, and this enables the reader to understand, with a minimum of effort, the basic principles underlying each disease.

The conditions dealt with are surgical affections of the abdomen and genitourinary tracts. As the authors emphasize, it is not fitting that one consider the infant a small adult, for in the category of congenital diseases no counterpart is found in older patients. Furthermore, in diseases common to young and old alike, a reduction of mortality in the former has been possible only by methods other than those used for the older group. Surgeons who operate on infants and children must therefore adopt a different set of standards for such patients, and this book is an excellent guide to exact diagnosis and proper therapy.

The very striking record at the Children's Hospital in the treatment of appendicitis in childhood makes this chapter alone worth the price of the book. The surgeon, pediatrician and general practitioner will all find the book of value in their practice.

*The Man Who Lived for Tomorrow: A biography of William Hallock Park, M.D.* By Wade W. Oliver, M.D. 8°, cloth, 507 pp., with 1 portrait. New York: E. P. Interton and Company, Incorporated, 1941. \$3.75.

This biography of the pioneer leader in bacteriology applied to public health, whose labors in the diagnostic field in the early days of the New York Health Department afforded a stimulus to laboratory procedure throughout America, is a charming and friendly account of the man and his work. Park's work on the laboratory diagnosis of diphtheria, published in 1893, was the first large-scale, intensive attack on the carrier problem and started a development that grew into a model city health department. Other work followed in order: smallpox vaccination, diphtheria antitoxin, the examination of milk by the Schick test and much else. Park was an indefatigable worker and set a high standard for himself and his colleagues. He is honored by a fitting and well-written biography.

*Vocational and Professional Monographs. No. 4. Medicine.* By Dwight O'Hara, M.D. 8°, paper, 27 pp. New York: Bellman Publishing Company, Incorporated, 1941. 50c.

This small brochure is addressed to college men who are considering entrance into the medical profession as a career. It is full of sound advice and the necessary facts that are needed in making the decision. The professions are clearly set forth in a readable, businesslike style. The material deserves a better format, for the author has created an exceptional essay, full of sound common sense. Apt quotations enliven the statistics, and many a man ready in the profession could read this little book with profit and pleasure.

(Notices on page x)

# The New England Journal of Medicine

Copyright, 1942, by the Massachusetts Medical Society

VOLUME 226

MAY 21, 1942

NUMBER 21

## SARCOMA OF THE BREAST

### A Report of Twenty-two Cases

HORATIO ROGERS, M.D.,\* AND SPENCER FLO, M.D.†

BOSTON AND GREENFIELD, MASSACHUSETTS

RECENT studies show that sarcoma constitutes between 2 and 3 per cent of all malignant tumors of the breast, but since the medical literature of the past eighty years records less than 600 cases,<sup>1</sup> it seems that the diagnosis is often missed.

The combined records of the Pondville Hospital (Massachusetts Department of Public Health) and Massachusetts General Hospital back to 1923 contain 22 cases of breast sarcoma with reliable pathological diagnoses and follow-up notes. All 22 patients were women between the ages of eighteen and sixty-nine, and the average age was forty-four years. Comparable figures in a group of 60 patients treated at the Johns Hopkins Hospital from 1894 to 1934 give forty-nine years as an average age, with a range of thirteen to seventy-five years<sup>2</sup>; there were 2 male patients.

#### Classification

The terminology resulting from different pathological classifications is confusing to the surgeon. A practical and comparatively simple classification is suggested by Fox,<sup>2</sup> who divides all breast sarcomas into four groups as follows:

#### Group I. Fibrosarcoma

- (a) Fascial type (spindle-cell sarcoma, periductal angiosarcoma and fibrosarcoma)
- (b) Secondary to adenofibroma (adenofibrosarcoma)
- (c) Secondary to intracanalicular fibromyxoma (periductal myxosarcoma,<sup>3</sup> fibromyxosarcoma and cystosarcoma)

#### Group II. Neurogenic sarcoma (perineural fibrosarcoma and melanotic sarcoma)

#### Group III. Lymphoid and myeloid sarcoma (round-cell sarcoma)

#### Group IV. Miscellaneous nonindigenous sarcomas (giant-cell sarcoma, carcinosarcoma, angiosarcoma, liposarcoma and so forth)

Group I (fibrosarcoma) is by far the largest, containing 82 per cent of our cases and 70 per cent of those at the Johns Hopkins Hospital. The individual tumors in this group vary somewhat in degree of malignancy, but their clinical behavior is fairly constant and comparatively favorable. They tend to form large bulky tumors, to grow into contiguous structures by direct extension, not to metastasize to regional lymph nodes and not to invade the blood stream until late, if at all.

The other groups are less important because they include so few cases. The neurogenic sarcomas and the lymphoid and myeloid sarcomas are characterized by a high degree of malignancy and a fatal outcome. There are rapid growth, early metastasis to regional lymph nodes (especially in the lymphoid and myeloid types), early blood-stream invasion and early remote metastasis. The last group contains miscellaneous rare tumors whose behavior shows no group characteristics.

In Table 1, our 22 cases are compared with those reported by Fox. Approximately one third of the patients in both series are known to be dead of sarcoma, the two mortality rates being strikingly similar. The rate of curability is less accurate, since it is based on an arbitrary time limit of five years. On this basis, the curability for our series of 22 patients is not lower than 36 per cent, and that for the 18 patients in Group I (fibrosarcoma) is not lower than 44 per cent. A scrutiny of our 6 indeterminate cases shows that at least 3 are likely to be cured; this will raise the curability figures to 50 and 60 per cent, respectively. It is recognized that our figures are too small for the derivation of significant percentages.

\*Instructor in surgery, Harvard Medical School; associate visiting surgeon, Massachusetts General Hospital.  
†Formerly, resident surgeon, Pondville Hospital.

All 4 of our patients outside Group I died of sarcoma. To what extent this mortality rate should be ascribed to inadequate treatment and how accurately it reflects the fatal nature of the disease

TABLE 1. *Tabulation of Cases.*

TYPE	STATUS OF PATIENT	OUR CASES	FOX'S CASES
Group I (fibrosarcoma)	Dead of sarcoma	4 (22%)	10 (24%)
	Living and well at 5 years	8 (44%)	14 (33%)
	Living and well under 5 years	6	18
	Totals	18	42
Group II (neurogenic sarcoma)	Dead of sarcoma	0	3
	Living and well at 5 years	0	0
	Living and well under 5 years	0	4
	Totals	0	7
Group III (lymphoid and myeloid sarcomas)	Dead of sarcoma	1	5
	Living and well at 5 years	0	0
	Living and well under 5 years	0	2
	Totals	1	7
Group IV (miscellaneous sarcomas)	Dead of sarcoma	3	1
	Living and well at 5 years	0	0
	Living and well under 5 years	0	3
	Totals	3	4
All groups	Dead of sarcoma	8 (50%*)	19 (58%*)
	Living and well at 5 years	8 (50%*)	14 (42%*)
	Living and well under 5 years	6	27
Grand totals		22	60

\*These percentages take no account of the cases followed for less than 5 years

itself cannot be determined. It will be noted that the Johns Hopkins series also shows no five-year cures outside Group I.

The treatment of these 4 cases happened to be inadequate. Two patients had local excision of small tumors, one of which proved to be a lymphoid sarcoma, and the other, a carcinosarcoma. The former refused further surgery and, after temporary improvement with x-ray treatment, died of multiple generalized metastases within six months. The latter died of metastases to the ribs, lungs and brain twenty months after a fruitless radical mastectomy undertaken after an unexplained delay of ten months. Both the remaining 2 patients had large angiosarcomas, one with known lung metastases. Palliative simple mastectomy was done for both. One died in two years of generalized metastases, and the other in six months of metastases to the lymph nodes and lungs. Thus, no conclusions concerning the possible ef-

fectiveness of ideal treatment can be drawn from these 4 cases.

A consideration of the treatment of the 18 cases in Group I (fibrosarcoma) is more instructive. Of 2 patients who had local excision of small tumors, one is alive after sixteen years, and the other, although she has survived operation for only four and a half years, is probably cured since no tumor tissue could be found when a wide excision of the scar was done ten months after the original operation.

Of the 11 patients treated by simple mastectomy, the 4 whose tumors were small (under 7 cm.) are alive—2 for over five years and 2 for over two years. A fifth patient with a tumor of unrecorded

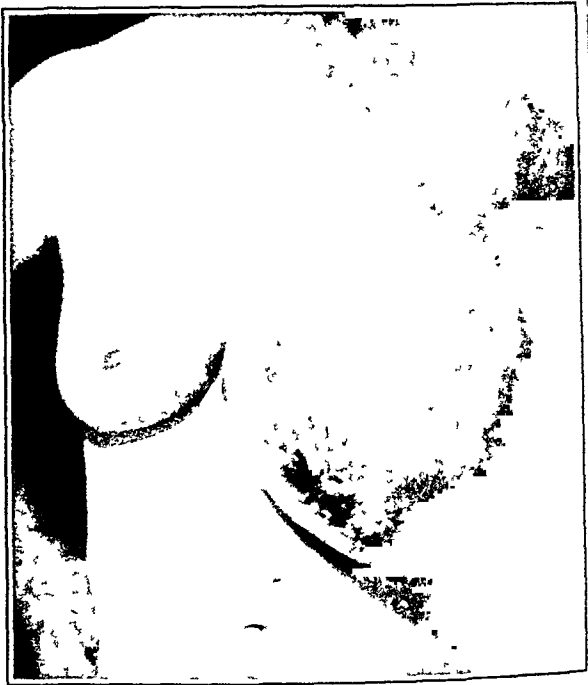


FIGURE 1.

*This sixty-four-year-old patient had had painless swelling of the breast for nine months. The pathologist reported "adenofibrosarcoma." The patient was living and well five years and three months after simple mastectomy.*

size had simple mastectomy followed in two years by local recurrence in the form of a tumor 26 cm. in diameter. This was radically excised, and the patient is living and well three and a half years later (five and a half years after simple mastectomy). Of the remaining 6 patients, whose tumors were large (10 to 30 cm.), 3 are living after ten, five and a half, and two years, respectively. The other 3 died, 1 in two years of extension to pleura, 1 in two years of bone metastases, and 1 in six months of pulmonary metastases.

Radical mastectomy was undertaken as a primary procedure in only 4 cases. The 2 patients

whose tumors were small are alive and well after nine and seven years, respectively. Of the 2 patients whose tumors were large, one is alive for four years; the other was subjected to radical



FIGURE 2.

*This thirty-three-year-old patient had had painless swelling of the breast for about seven years. The pathologist reported "fibrosarcoma of breast and benign hyperplasia of lymph node." The patient was living and well two years after simple mastectomy, with lymph-node biopsy.*

mastectomy on the chance that a suspicious area of bone destruction in the jaw might prove to be unrelated to her disease, but she died six months later with metastases to the jaw and scapula. It is



FIGURE 3.

*This sixty-year-old patient had had a simple mastectomy for painless swelling of six months' duration, associated with trauma to the breast. The pathologist reported "adenofibrosarcoma." Nine months later, a radical operation was done for local recurrence, and the photograph shows a second recurrence twenty months after the last operation.*

significant that the axillary lymph nodes were not affected in all 4 cases.

Finally, 1 patient whose operation is not well enough described to be classified lived ten and a half years and died of other causes.

### Treatment

In an evaluation of the results of treatment in these 22 cases, the most striking conclusion is as follows: for patients in Groups II (neurogenic), III (lymphoid and myeloid) and IV (miscellaneous), the only hope of cure lies in radical mastectomy and axillary dissection before bloodstream and lymphatic invasion has occurred.

It appears equally clear that this is not true of patients in Group I (fibrosarcoma). There is



FIGURE 4.

*This photograph of the patient in Figure 3 was taken eight months after a block excision of the chest wall, including three ribs and a portion of the pleura. There is a third local recurrence. The patient died four months later from extension of the tumor into the pleural and peritoneal cavities.*

evidence that axillary dissection is not necessary in this group. In none of our 18 cases were lymph-node metastases demonstrated, whereas unaffected lymph nodes were found in 9 cases. Furthermore, 6 patients whose axillary nodes were not removed are still alive. On the other hand, it seems unwise to rely on either local excision or simple mastectomy for cure. Since death from tumors of the fibrosarcoma group is due to extension of the tumor into fascia or blood vessels, at least the pectoral fascia and preferably the pectoralis muscle should be removed, as well as the breast. This procedure, which would have added little to the risk of simple mastectomy, would probably have prevented 2 of our 3 deaths and obviated a massive local recurrence in another case.

Undoubtedly the reason so-called "palliative simple mastectomy" is so often done for enormous tumors of the breast is that the surgeon is thinking in the more familiar terms of carcinoma, and it does not occur to him that so large a tumor could possibly be curable. Six of our Group I (fibrosarcoma) patients presented this picture and received this treatment, some with the preoperative diagnosis of "advanced cancer of the breast." Three are apparently cured, in spite of an inadequate operation. There is good reason to think that 5 of the 6 might have been cured if a curative rather than a palliative operation had been done.

### Diagnosis

The diagnosis of breast sarcoma depends on microscopic examination. Even for the pathologist, it is not always easy to recognize the different types of malignant tumor or even to tell whether a tumor is malignant or benign. All that the surgeon can do is keep in mind the possibility of sarcoma and remember that not all large tumors are incurable. A large tumor, particularly in the absence of palpable axillary nodes, is probably either a comedo carcinoma, benign tumor or fibrosarcoma. Neither the patient's age nor a story of trauma has any diagnostic value. The story of a small tumor that after having been the same size for several years suddenly begins to grow larger is suggestive of fibrosarcoma, but is not diagnostic. The presence of cystic areas, bluish discoloration of the skin and conspicuous dilated veins over a large, lobulated tumor is almost pathognomonic of sarcoma.

### Prognosis

In 8 fatal cases, the average duration of life after operation was seventeen months, the shortest three months, and the longest forty-one months. The average time from onset of symptoms to death was twenty-seven months, the shortest six months, and the longest forty-seven months.

No definite correlation can be found between prognosis and age, nor does the duration of symptoms furnish any reliable aid. The type of tumor appears to be of the greatest significance, tumors of the fibrosarcoma group offering the best prognosis; Group III (lymphoid and myeloid sarcoma) tumors offer the worst, and tumors of the other groups are in between.

The size of the tumor appears to have prognostic significance only in Group I (fibrosarcoma). With tumors less than 5 cm. in diameter, the ratio of dead to living patients was 0.5; between 5 and 10 cm., it was 1:3; and between 10 and 30 cm., it was 3:8.

### SUMMARY AND CONCLUSIONS

Twenty-two cases of breast sarcoma are reported, with a discussion of their classification, treatment and results.

Of 18 patients (82 per cent) whose tumors were classed as fibrosarcomas, 8 (44 per cent) are known to be cured for at least five years, 6 are living under five years, and 4 are known to be dead of sarcoma. Of 4 patients whose tumors were classed as lymphoid sarcoma, angiosarcoma or carcinosarcoma, all are known to be dead of sarcoma.

The treatment of choice for tumors of the fibrosarcoma type is surgical removal of the breast and pectoralis major muscle, without dissection of the axilla. If the tumor is small and has not invaded the blood stream, the prognosis is excellent.

The only possibility of cure for the other types of sarcoma is by early radical mastectomy with axillary dissection. Regardless of the size and short duration of the tumor, the prognosis is poor unless the tumor is a fibrosarcoma.

### REFERENCES

1. Geist, S. H., and Wilensky, A. O. Sarcoma of the breast. *Ann Surg.* 62:11-21, 1915.
2. Fox, S. L. Sarcoma of the breast, with a report of sixty cases. *Ann Surg.* 100:401-421, 1934.
3. Greenough, R. B., and Summons, C. C. Fibro epithelial tumors of the mammary gland. *Ann Surg.* 54:517-537, 1911.

## PNEUMONIA: A STUDY OF ONE HUNDRED AND THIRTY-TWO CASES TREATED IN THE HOME WITH SULFATHIAZOLE<sup>1</sup>

JOSEPH ROSENTHAL, M.D.,<sup>†</sup> WILLIAM A. MACCOLL, M.D. ‡ AND JOSEPH H. PRATT, M.D. §

BOSTON

**D**URING the winter of 1940-41, 132 patients with pneumonia were treated in their homes by the Domiciliary Medical Service of the Boston Dispensary. This free service by the Boston Dispensary was established in 1796 for care of the indigent sick in their homes. In a discussion of this service, Wing<sup>1</sup> states

The burden of home care of the sick who are unable to employ a physician is usually a responsibility of the local rather than of the state or federal government. It is commonly exercised as a function of the Public Welfare or Poor authorities rather than of medical institutions. Boston, unlike other cities of the country, has never employed city physicians for this purpose but has accepted the services of privately supported medical charity as a substitute.

The physicians on this service have two or more years of postgraduate hospital work and are appointed as fellows in medicine for one year. They spend their mornings in the Out Patient Department, and their afternoons, in making home visits. Their work is supervised by a full time physician who also acts in the capacity of consultant. Approximately 50,000 visits are made annually.

During the winter months, many cases of pneumonia are seen, and in the past, because of inadequate home facilities for the treatment of pneumonia then available, it was necessary to hospitalize most of these patients. This, no doubt, threw an additional burden on the already overcrowded hospitals in Boston. With the introduction of the sulfonamides, it seemed reasonable to believe that many of these patients could be successfully treated in their own homes. This led to the formation of the Pneumonia Service, consisting of four district physicians particularly interested in this work. These men were made available during and after their regular hours to study and treat patients in whom a diagnosis of pneumonia was made. Two physicians were designated to care for adults, and two for infants and children.

### METHODS

All cases of pneumonia or suspected pneumonia seen by the district physicians were referred through the district office to the physician on the Pneumonia Service, who visited the patient within a few hours. If the diagnosis of pneumonia was confirmed, the following course was instituted: the history was taken, and physical examination was made for corroboration of the diagnosis, sputum was obtained for typing, nose or throat swabs being taken in children, leukocyte and erythrocyte counts, and hemoglobin estimations were made, and blood films for differential counts were taken, a blood culture was obtained, and a urinalysis was made.

Following this, the treatment was begun at once. The drug chosen was sulfathiazole, because of its effectiveness and slight degree of toxicity.<sup>1-3</sup> It was assumed that patients were likely to follow the treatment carefully if such distressing symptoms as nausea and vomiting were eliminated. In most cases, an amount of sulfathiazole sufficient for twenty-four hours was supplied by the physician, and the first dose was usually administered in his presence.

The dosage in pneumonia in adults was 4 gm (60 gr) as an initial dose, followed by 1 gm every four hours, day and night, until the patient's temperature had been normal for seventy-two hours, although in some cases this was reduced to 1 gm every six hours during the afebrile stage, after which the drug was discontinued. In children, the initial dose was 0.065 gm (1 gr) per pound of body weight. Following this, a daily dosage of 0.065 gm per pound was administered daily, divided into six equal parts given every four hours, day and night, until the temperature had been normal for thirty-six hours, when the drug was discontinued.

Fluids were forced during the administration of the drug. Patients were instructed to take 3000 cc (3 quarts) of fluid daily. The output was followed. If the urine fell below 1500 cc in twenty-four hours, the cause was investigated, and additional fluid given. Recommended fluids consisted of stimulants, such as coffee, tea and Coca Cola, fluids high in carbohydrate, such as fruit

<sup>†</sup> From the Boston Dispensary District Service and the Department of Medical and Pediatric Tufts College Medical School.  
<sup>‡</sup> Medical supervisor of Boston Dispensary District Service and instructor in medicine Tufts College Medical School.  
<sup>§</sup> District physician on Boston Dispensary District Service as assistant pediatrician, Tufts College Medical School.  
<sup>1</sup> This is an abstract of Joseph H. Pratt's diagnosis. Hospital professor of diseases of the Tufts College Medical School.

<sup>1</sup> Sputum and blood cultures were examined in the Bacteriology Laboratory of the Massachusetts Department of Public Health.



juices, and mineral-containing liquids, such as broth, soup and bouillon made from cubes (each cube containing 2 or 3 gm. of salt). In children, a simple mixture of 3 tablespoonfuls of carbohydrate (sugar, Karo and so forth) and 1 teaspoonful of salt in 500 cc. (1 pint) of water was used to give approximately 5 per cent glucose and saline.

The patients were followed daily until complete recovery. If residual chest signs persisted, the patient was referred to the Out-Patient Department for a roentgenogram of the chest. After careful consideration, it was decided not to determine the blood sulfathiazole levels, and our experience shows that it was not necessary.

Supportive treatment consisted mainly of high-calorie diets, sedation for chest pain, general nursing care and, not the least important, the tender ministrations of the patient's own family. The assistance rendered to the patients and the district service by the Community Health nurse in this respect cannot be too highly praised. No oxygen, digitalis or artificial stimulants were used during the course of home treatment.

RESULTS

Age

The ages ranged between two months and eighty-six years. Approximately half the patients were below the age of twelve; 23, or approximately 17 per cent of the entire group, were above the age of fifty. Three patients were between eighty and ninety years of age.

Sex

Seventy-four (56 per cent) of the entire group were males, and 58 (44 per cent) were females.

Duration of Illness before Treatment

In pneumonia, the value of early treatment needs no comment. Because in most cases the patients were seen early, the treatment could be

TABLE 1. Duration of Illness before Treatment.

Days	No. OF CASES
1/2 or less	9
1	46
2	30
3	22
4	13
5	4
6	3
7	4
8	1
Total	132

instituted as soon as the physician on the Pneumonia Service had confirmed the diagnosis of the attending physician. Table 1 shows that in the majority of cases the treatment was instituted with-

in forty-eight hours after the onset of the illness; 9 patients were treated within twelve hours of the onset. Such factors as objection to hospitalization, family consultation, arrangements for care of children, waiting for ambulances and the necessary delay in examination and admission to the hospital are eliminated by home treatment.

Typing of Sputum

Pneumococci were found in the sputum of 70 cases (53 per cent) of the total of 132. In some patients who showed no pneumococci in the first sputum examination, a second sample was obtained, but this was positive in only 1 case. Table 2 shows the distribution of positive sputums by

TABLE 2. Types of Pneumococci Recovered.

TYPE	No. OF CASES
1	11
5	9
8	8
2	5
4	4
6	4
3	3
14	3
29	3
33	3
7	2
9	2
15	2
20	2
23	2
10	1
13	1
16	1
18	1
17	1
38	1
31	1
Total	70

types. Sixty per cent of the patients with positive sputums were above the age of twelve years. In evaluating the clinical data, we compared the patients whose sputum showed pneumococci with those in whom none were found.

Signs and Symptoms

In general, the signs and symptoms were similar in both groups of patients. The commonest presenting symptoms in the patients with pneumococci in the sputum were pain (67 per cent), dyspnea (63 per cent), frank chills (51 per cent) and bloody sputum (33 per cent). In all but the oldest age group, the clinical appearance presented was that of an extremely acute illness.

Temperature, Pulse and Respirations

The initial temperatures, pulses and respirations showed nothing remarkable and were characteristic of the disease in most cases.

Blood Cultures

An initial blood culture was obtained in every case but 1. Positive blood cultures were present in 6 cases. In a sixty-four-year-old patient, a Type

8 pneumococcus was found in the sputum, and blood culture was negative. Examination during a relapse a few days later showed a Type 8 pneumococcus in the sputum, and another blood culture was positive for Type 8 pneumococcus. In another case, a sixty-seven-year-old man (Case 10) first seen on the seventh day of his illness, had no pneumococci in the sputum, but a Type 2 pneumococcus was recovered from the blood culture. He expired on the day after treatment was started. In another case, there was a Type 5 pneumococcus in the sputum, and a similar type in the blood. One patient had a Type 1 pneumococcus in the sputum and blood. A twenty-two-month-old child, who showed no pneumococci in the sputum but had a positive blood culture,—Type 18,—made an uneventful recovery after three days; further treatment was refused by the family at the end of this time. Another patient, a five-year-old child, who showed no pneumococci in the sputum but Type 1 pneumococcus in the blood, made an uneventful recovery after three days of treatment. The mortality of the small group of cases with positive blood cultures was 17 per cent.

#### Blood Examinations

The initial white-cell counts ranged from 2000 to more than 50,000. A leukopenia was not considered a contraindication for sulfathiazole therapy. Red-cell counts and hemoglobin determinations showed normal variations. After therapy in most cases, there was a definite drop in the white-cell count, but there was leukopenia in only 1 case. In this patient, the white-cell count fell to 3800 per cubic millimeter, with 44 per cent granulocytes after three days of treatment, but with continued therapy, the count rose to 10,700.

In Case 10, mentioned above, the initial white-cell count was 2000; a second count taken on the day after therapy was instituted showed a rise to 3400, although the patient died on that same day. No marked drop in hemoglobin or red-cell count was noticed.

#### Urinalyses

Very few complications referable to the urinary tract were observed throughout the treatment. One outstanding feature was that in 40 patients the initial urinalyses showed the presence of albumin, white blood cells, red blood cells or casts or various combinations of them. This, in almost every case, cleared up rapidly under therapy with sulfathiazole. Twenty-four patients showed sulfathiazole crystals in the urinary sediment during treatment.

One patient showed gross hematuria. Sulfathiazole was stopped, and the urine became clear after about a week. A small group of patients

showed microscopic blood, which cleared up after treatment was stopped. There were no cases of anuria, and although it was rather difficult to measure correctly the fluid intake and output, we can safely say that in none of these cases was there evidence of retention of fluid in the tissues.

#### Duration of Fever

An interesting factor to be considered is the interval between the institution of therapy and the

TABLE 3. Duration of Fever.

DURATION hours	No. OF CASES
CASES WITH PNEUMOCOCCI	
24 or less	23
36	3
48	21
60	1
72	7
Over 72	15
Total	70*
CASES WITHOUT PNEUMOCOCCI	
12 or less	2
24	37
36	0
48	17
60	1
72	4
Over 72	1
Unknown	1
Total	66*

\*The additional 4 cases represent relapses

drop in temperature to normal. The average length of time before the temperature dropped to normal was about forty-eight hours (Table 3).

#### Total Dosage of Sulfathiazole

Two groups of patients are considered: those who showed pneumococci in the sputum, and those who did not. Furthermore, adults and children are considered separately.

It was found that in the typed cases, adults received an average of 37 gm. of sulfathiazole, and children required an average of 12 gm. In the nontyped cases, adults received an average of 23 gm., and children an average of 10 gm.

#### Duration of Treatment

The average actual duration of treatment in the home seems to be less than that in patients treated at the hospital. It is quite possible that in many of these cases at home, as soon as the patients seemed to be well clinically, there was a tendency on the part of the family to stop all medication. This apparently had little effect on the ultimate outcome of the disease.

Since there was no direct control over the administration of the drug and since family co-operation was not always complete, the physician usually gave the initial large dose before leaving the patient. Platt<sup>13</sup> has suggested that a single large dose is frequently therapeutically effective, and in several cases, this proved to be so.

The average duration of treatment—not including fatal and hospitalized cases—was 4.0 days for the adults and 3.6 days for the children who had pneumococci in the sputum; among the patients who did not have pneumococci in the sputum, the average duration was 3.8 days for adults and 3.4 days for children.

### *Toxic Symptoms*

The outstanding toxic symptom observed in these cases was vomiting, which was noted in 20 cases. It was quite evident that in some of these the vomiting was due to the disease rather than to the drug, since it also occurred before treatment. In no case did this symptom become a serious problem. Three patients had some abdominal distention, which might or might not have been due to the drug.

A papular rash on the face and trunk was observed in one case, and a nodular erythematous rash on the extremities in another. Gross hematuria occurred in 1 patient, and microscopic hematuria in a few, as mentioned above.

A rise of temperature that could definitely be attributed to sulfathiazole was not noted in any of the cases, possibly because of the short duration of treatment.

### *Complications*

One patient developed, on the third day, a pleural friction rub over the involved portion of lung. It disappeared after four days. One patient stricken with pneumonia in her third month of pregnancy made an uneventful recovery. A twenty-eight-year-old man with a Type 3 pneumococcus in the sputum who was hospitalized because of poor home conditions developed an empyema at the hospital and was treated by thoracotomy. A thirty-five-year-old man with a Type 1 pneumococcus developed evidence of fluid in the chest after a week of treatment, and this was found to be due to a serous pleurisy. He was hospitalized, and chest taps showed no evidence of empyema. He was discharged on the ninth hospital day following an uneventful recovery.

Four infants had pertussis in addition to pneumonia. One patient developed diabetic acidosis and had to be hospitalized. Altogether, 11 patients in the entire group had to be hospitalized for various reasons.

### *Deaths*

The 5 fatal cases seem worthy of individual comment.

CASE 10. W. D. (B. D. D. 88711), a 67-year-old man, was treated for cirrhosis of the liver in August, 1940, at the Boston City Hospital. This patient, who was a chronic alcoholic, was seized with pain in the right chest on the

evening of December 25, 1940, and then with fever and increase of cough. He had had a common cold for several days previously. He was first seen by a district physician on December 31. The temperature was 102.4°F., and the pulse 120. A mistaken diagnosis of influenza was made. On January 1, 1941, the temperature was 100.4°F., the respirations 40, and the pulse 140. Lobar pneumonia involved both lower lobes. The white-cell count was 2000. On prolonged examination of the smear, only 1 neutrophil, 9 lymphocytes and 2 monocytes were found. The urine contained a large trace of albumin, numerous casts and 1.4 per cent sugar. No pneumococci were found in the sputum. A Type 2 pneumococcus was grown from the blood. Sulfathiazole, begun on January 1, the 8th day of the illness, was discontinued after a day owing to the leukopenia and nephritis. This was a mistake, since the blood on January 2, after 9 gm. of sulfathiazole had been given, contained 3400 leukocytes, of which 18 per cent were neutrophils. The urine on January 2 was free from sugar. The patient died the following night.

CASE 14. J. W. (B. D. D. 111921), a 41-year-old man, complained of fever, chilly sensations and aching pains in the extremities on December 26, 1940—5 days before treatment with sulfathiazole was begun. On the following day, there was a cough, with copious tenacious brownish sputum; the patient was a chronic alcoholic, and his landlady stated that he was probably drinking throughout the early part of his illness. The temperature was 102°F., the respirations 38, and the pulse 120. Pneumonia of the right middle and lower lobes was found. A Type 5 pneumococcus was found in the sputum and blood. Since the patient failed to improve, he was sent on January 3 to the Massachusetts Memorial Hospitals, where in addition to the sulfathiazole he was given 300,000 units of antipneumococcus (Type 5) serum after a blood culture on January 3 was found to be positive. He failed to gain and died on January 14, the 26th day of his illness.

CASE 47. N. B. (B. D. D. 83850), an 83-year-old man had been under treatment for chronic congestive failure of the heart for over 2 years when, on January 12, 1941 he was seized with a shaking chill lasting 2 hours and followed by fever. When seen on the following day, he had a cough and was raising yellow sputum. The temperature was 100°F., the respirations 32, and the pulse 92. The patient was dyspneic. Bronchopneumonia of both lower lobes was found. The white-cell count was 21,100. A Type 9 pneumococcus was found in the sputum. The blood culture was negative. Sulfathiazole treatment was begun. In 24 hours, the temperature fell to 98°F., the respirations to 24, and the pulse to 74. On the following day, the patient was greatly improved, and there was no dyspnea. The temperature was 98.2°F., and the pulse 71. The temperature was normal for 5 days—from January 14 to 19. Then, there was a recurrence of fever and pneumonia. The patient died on January 24, the 13th day of his illness.

CASE 128. A. B. (B. D. D. 95716), a 79-year-old man toward the end of March, 1941, was found to have cerebral thrombosis, with increased weakness of the left side of the body and toes. He also had chronic heart failure and senility. He had had hemiplegia a year previously. On April 5, cough, fever and labored breathings were noted. On April 9, the patient was semicomatose. He was first seen on April 10, when the temperature was 100°F., the respirations 40, and the pulse 80. Pneumonia of the right lower and left upper and lower lobes was found. Treatment with sulfathiazole was begun. The total amount

given during 6 days was 40 gm. No pneumococci were found in the sputum, and the blood culture was sterile. The patient did not respond to treatment and died on April 16 the 12th day of the disease.

CASE 153. M. M. (B. D. D. 119301), a 77 year old woman was seized with a shaking chill, followed by fever and cough on January 21, 1941. The patient had had congestive heart failure during the previous year. She was first seen on January 23, when the temperature was 102°F, the respirations 32, and the pulse 100—the rate at the apex being 120. Auricular fibrillation was present. Pneumonia involving both lower lobes was found. The heart was slightly enlarged on percussion. The liver edge was felt three fingerbreadths below the costal margin. There was no sputum but a swab made from the pharynx yielded Type 5 pneumococci. The blood culture was negative. Treatment with sulfathiazole was begun on January 24. The patient was too weak to move in bed and was incontinent and semicomatose, the eyes were sunken and glazed. She was sent to the Boston City Hospital apparently moribund. She lived however, until February 7 the 20th day of her illness. Autopsy revealed a lobar pneumonia, general arteriosclerosis, cardiosclerosis and chronic pulmonary tuberculosis involving both apices.

### Response of Children

The response of infants and children to treatment in the home was especially satisfactory. Most parents were very co-operative in following directions, and the supportive measures and general care were adequately administered. The absence of the psychic trauma of removal to unfamiliar surroundings was believed to be a positive factor in the success of home treatment. The absence of abdominal distention, except in 2 infants, suggests that the emotional strain attending hospitalization may be a causative element in the development of this complication. Convalescence appeared to be a more pleasant period, and hence more tolerable, when the patient was surrounded by familiar toys and faces. No difficult problems in child management peculiar to the treatment of pneumonia in the home arose.

### SUMMARY AND CONCLUSIONS

One hundred and thirty-two cases of pneumonia were successfully treated in the home during the winter months under adverse conditions, as the total mortality (5 patients, or 3.8 per cent) indicates. Pneumococci in the sputum were obtained in 70 cases, and 6 patients had positive blood cultures.

The mortality rate for cases with pneumococci in the sputum was 6 per cent. There were very few toxic manifestations due to the drug, and no cases of hemolytic anemia or granulopenia. Few urinary complications and no fever due to the drug were noted.

This work represents a financial saving to the community of several thousands of dollars that would have been incurred if these patients had been treated in hospitals.

The study indicates that pneumonia may be treated at home by the use of sulfonamides with death rates as low as or lower than those obtained in hospital practice, provided treatment is begun early in the disease.

During the winter season of 1941 and 1942 85 additional cases of pneumonia were treated with sulfadiazine with only 1 death. That was in a seventy-five year old woman who during the course of treatment, developed marked abdominal distention was hospitalized and died on the third hospital day, a post mortem examination disclosed partial intestinal obstruction due to a carcinoma of the small bowel with extensive metastases to the lungs and liver, and massive bilateral pneumonia.

### REFERENCES

1. W. F. E. Medical care of the sick, the homes, B. H. Am. Ho. p. 9 (Apr. 1) 25 33 1935. Revised Medical Care of the Sick, N. H. Am. Ho. p. 31 pp. Bos. on Bo. on Dispensary 1940.
2. Finland M. Treatment of pneumonia. *New Eng. J. Med.* 223: 499 506 1940.
3. Blake F. G. The treatment of pneumococcal pneumonia. *New Eng. J. Med.* 223: 661 66 1940.
4. Vol. 1. F. L. E. T. R. O. and O. N. C. H. B. Sulfathiazole in the treatment of pneumococcal pneumonia: a comparative study utilizing sulfapyridine therapy. *Am. J. M. Sc.* 200: 8784 1940.
5. Finland M., Lowell F. C. and Strauss E. Treatment of pneumococcal pneumonia with sulfapyridine, sulfathiazole and serum: analysis of the results of specific therapy at the Boston City Hospital from July 1939 through June 1940. *Ann. Int. Med.* 14: 1184 1198 1941.
6. Flippin H. F., Reinhold J. G. and Schwartz L. Sulfapyridine and sulfathiazole therapy in pneumococcal pneumonia. *J. A. M. A.* 116: 683 690 1941.
7. Spink W. W. and Hansen A. E. Sulfathiazole clinical evaluation. *J. A. M. A.* 115: 840 847 1940.
8. Pepper D. S. and Ham G. C. Sulfathiazole treatment in respiratory infections. *Am. J. M. Sc.* 200: 84 90 1940.
9. Flippin H. F., Rose S. B., Schwartz L. and Domm A. H. Sulfadiazine and sulfathiazole in the treatment of pneumococcal pneumonia: a progress report on two hundred cases. *Am. J. M. Sc.* 201: 585 597 1941.
10. Carey U. W. The treatment of pneumonia in infants and children. *J. Pediatr.* 18: 153 161 1941.
11. Scott J. P. and Jones A. M. Sulfathiazole in the treatment of pneumonia in infants and children: a report on one hundred and sixty-seven patients treated with sulfathiazole and a comparison with ninety-three patients treated with sulfapyridine. *J. Pediatr.* 17: 423 434 1940.
12. Finland M. Chemotherapy of pneumonia with special reference to the present status of sulfadiazine. *New Eng. J. Med.* 223: 187 193 1941.
13. Platt L. Treatment of pneumonia in children with a single dose of sulfapyridine. *Am. J. Dis. Child.* 60: 1019 1074 1940.

## ELECTROENCEPHALOGRAPHIC STUDIES IN CHILDREN PRESENTING BEHAVIOR DISORDERS\*

LAZARUS SECUNDA, M.D.,† AND KNOX H. FINLEY, M.D.‡

BOSTON

**I**N CHILDREN and adolescents presenting behavior disorders, the relative consequence of environmental and biologic factors in the individual case should be determined, since the more capable one is of evaluating these factors in patients, the more intelligent the therapeutic approach will be.

Smith<sup>1</sup> has found that the development of the electrocortical activity of infants follows the course of the myelinating cerebrum. The electroencephalogram can therefore be used as a valuable measure of the structural and functional maturity of the brain.

Lindsley<sup>2</sup> and Smith<sup>3</sup> have shown that the adult pattern of the electrical brain potentials is not established until late childhood or early adolescence. They have demonstrated, and we have been able to confirm, from our own studies, that there are individual variations in the age in which the adult pattern is stabilized.

Jasper, Solomon and Bradley,<sup>4</sup> in their studies of childhood behavior disorders, noted that 71 per cent of the patients had abnormal electroencephalograms. Half the abnormal tracings were found in cases in which there was no other objective evidence of cerebral dysfunction. Strauss, Rahm and Barrera<sup>5</sup> observed abnormal electroencephalograms in 59 per cent of 22 children with primary behavior disorders. Lindsley and Cutts,<sup>6</sup> from their study of "constitutionally inferior" and behavior-problem children, found the electroencephalograms different from those of normal children in three ways: high alpha cycles, with 2 to 5 cycles per second; an increase in the number of 5 to 8 cycles per second; and vulnerability of the testing pattern to hyperventilation. These studies indicate that in a high percentage of behavior-problem children, one is dealing with an immature or abnormally functioning cerebrum. Hence, the electroencephalogram may afford an objective measure of the physical immaturity of the brain.

At the Boston Psychopathic Hospital, we have obtained tracings on 143 children presenting behavior disorders (106 boys and 37 girls). Sixty-

eight were sent by the courts of Greater Boston for psychiatric study. Seventy-five were referred by physicians at the request of their parents; thirty-five of these children came from foster parents.

Of the 143 children, 125 had normal physical and neurologic findings and no history of an illness involving the central nervous system. Seven

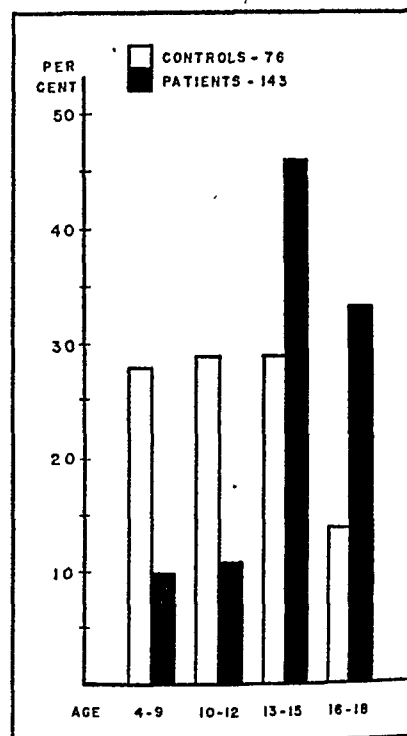


FIGURE 1. *Percentage Distribution of Controls and Patients in Age Groups.*

had histories of head injury followed by a period of unconsciousness; 6 had histories of chorea; 3 had a questionable history of encephalitis; and 2 may have had seizures prior to the age of seven. The average intelligence quotient of the group was 87, with a range from 65 to 134. Indication of a poorly integrated personality was brought out by the number who had a history of neurotic traits (enuresis, nail biting, and walking and talking in their sleep). Ninety had one or more neurotic traits, 32 had none, and in 21 no information was given.

The influence of the child's position in the sibling group did not seem to play a very significant role, for just as many occupied an intermediate

\*This work was supported from grants by the Scottish Rite Mason Fund and the Proctor Fund, Harvard Medical School.

†From the Boston Psychopathic Hospital and the Department of Psychiatry, Harvard Medical School.

‡Assistant in psychiatry, Harvard Medical School; senior physician, Boston Psychopathic Hospital; captain, Medical Corps, United States Army.

§Instructor in psychiatry, Harvard Medical School.

position as those who were the oldest, youngest or only child.

The family background revealed only 18 normal families. Of the 143 patients, 16 had psychotic parents, 4 had a family history of epilepsy, and 76 came from homes broken because of desertion, divorce or death of parents, 36 of the last being referred from foster homes. Parents of 43 were chronic alcoholics, parents of 43 were openly hostile, and those of 28 were oversolicitous. A striking fact is that only 17 patients had other siblings who were behavior problems.

The problems that led to admission were many. Forty six were admitted for stealing, 33 for sexual

puberty; therefore, our groups were built around this age range. Four groups were chosen: four to nine as the childhood period; ten to twelve as the preadolescent period; thirteen to fifteen as the early adolescent period, and sixteen to eighteen as the late adolescent period. Figure 1 shows the distribution of patients and controls.

Since we were dealing with an age range in which the normal electroencephalogram differs from the adult pattern and varies from year to year in its development into the adult pattern (Smith,<sup>3</sup> Lindsley<sup>2</sup> and Gibbs and Gibbs<sup>8</sup>), we obtained tracings on 76 control children (69 boys and 7 girls) of the same age range as the group

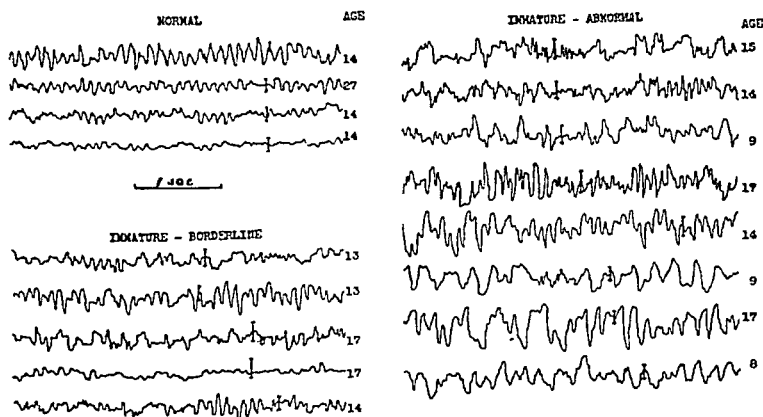


FIGURE 2 Samples of Normal, Immature Borderline and Immature Abnormal Electroencephalographic Tracings

Most of the samples were taken from the older age groups. Some of the samples in the immature borderline group, for example, the second one, would be considered normal in a child of six or seven. The vertical lines through the tracings represent 50 microvolts. It should be noted that the degree of amplification varies in the different tracings.

misbehavior, 32 for being runaways and 21 for temper tantrums; 15 were called "stubborn children" by the courts, 13 were truants, 9 set fires and 5 were depressed. A number of children had more than one type of undesirable behavior.

All the children adjusted themselves well on the wards and gave no evidence of being behavior problems, except for 21 who were overactive, sulky, vindictive, noisy or destructive, or had temper tantrums when verbally reproached.

Since a study of juvenile delinquency by the Gluecks<sup>7</sup> stressed the fact that delinquency decreases with increase in maturity, it seemed advisable to divide the cases into age groups. The majority of patients were between the ages of thirteen and fifteen. This age range is a particularly vulnerable period, owing to the onset of

of behavior problem children. They were selected from a middle class population, and to the best of our knowledge, they were from good homes and environment and were not recognized as presenting any problem at home, in school or in the community. Intelligence quotients were not available, but we estimate that the children were at least of average intelligence.

#### APPARATUS AND PROCEDURE

The records were obtained with a Grass six-channel electroencephalographic apparatus. Electrodes were placed over the frontal, precentral and occipital regions of each hemisphere, the indifferent electrode being placed over the mastoid. Two types of records were obtained: six simultaneous recordings from each of the frontal, pre-

central and occipital areas of the two hemispheres, grounded to the indifferent mastoid electrode; and six simultaneous bipolar records, including the left frontal to left precentral, right frontal to right precentral, left precentral to right precentral, left precentral to left occipital, right precentral to right occipital, and left occipital to right occipital. The records were obtained with the patient lying down and with the eyes closed. Hyperventilation for a period of two minutes was done in all the controls and in most of the patients.

#### ANALYSIS OF RECORDS

The tracings are divided into three groups: normal, immature-borderline and immature-abnor-

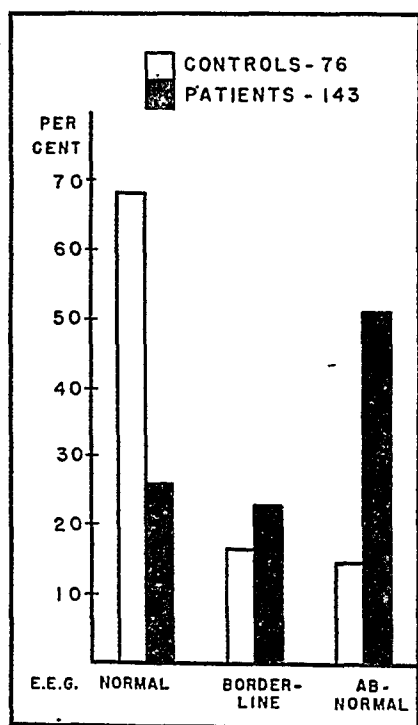


FIGURE 3. Percentage Distribution of Normal, Immature-Borderline and Immature-Abnormal Electroencephalographic Tracings from Patients and Controls.

*Normal tracings are much less common in the behavior-disorder group.*

mal (Fig. 2). Because of the normal immaturity of the pattern in childhood and early adolescence, it is impossible to say whether an atypical pattern at a given age represents a delay in the maturity of the pattern or whether it is secondary to some congenital or acquired injury to the brain. It would be incorrect to label a patient's brain waves as abnormal when the unusual activity might be due only to a delay in his maturity. Consequently, when patterns are not normal for a given age, we prefer to consider them either immature-borderline or immature-abnormal, depending on the degree to which they deviate from the normal

pattern of that age range. The evaluation of hyperventilation in children is complicated by the fact that normally the brain potentials are more vulnerable to this procedure than those of adults. This vulnerability decreases with increase in age. We have used our controls as a guide in evaluating the response to hyperventilation in the patients.

Recently, Davis and Wallace<sup>9</sup> have demonstrated that brain potentials in normal persons who tend to run low blood-sugar levels or who have not eaten for several hours are vulnerable to hyperventilation. Since all our control records were obtained at five o'clock in the evening (four to five hours after lunch time), whereas most of the patients' records were obtained between one and two o'clock (one or two hours after lunch time), our controls were overweighted, so far as anomalies of hyperventilation, resulting from a low blood sugar, are concerned.

#### RESULTS

Of 143 children presenting behavior disorders, 26 per cent had normal, 23 per cent borderline and 51 per cent abnormal electroencephalograms; whereas of the 76 controls, 68 had normal, 17 had borderline and 15 per cent abnormal tracings (Fig. 3). As a group, the electroencephalograms of the behavior disorders were more vulnerable to hyperventilation than those of the controls (Table 1). This finding is in agreement with the conclusions of Lindsley and Cutts.<sup>6</sup>

The controls and the patients were divided into age groups; and the percentages of normal, im-

TABLE 1. Response of Electroencephalogram to Two Minutes of Hyperventilation.

TYPE OF CASE	NO RESPONSE	MODERATE RESPONSE	MARKED RESPONSE
	%	%	%
Controls (71 cases)....	44	27	29
Behavior problems (42 cases)....	23	33	44

mature-borderline, and immature-abnormal records that occurred in each age group were compared. Moreover, when one compared age group with age group, there was, on the whole, a progressive increase in normal records and a diminution in abnormal records with increase in age (Fig. 4). There was no significant difference in the percentage of behavior-disorder children with abnormal records who were adjusted on the ward and those who continued to exhibit maladaptation.

Twenty-four (16 per cent) of the children with behavior disorders had inferior intelligence; and of these, 15 (62 per cent) had abnormal tracings. Of the 119 who had normal intelligence, 59 (50 per cent) had abnormal tracings. This is not a significant difference.

## DISCUSSION

This study demonstrates that the electrocerebral activity of many children with behavior disorders is not normal. A wave of slow rate is the commonest abnormal finding in these patterns. In the adult, such a wave is definitely abnormal, but in early childhood slow activity is a normal finding; therefore, a greater degree of slow activity than

to adjust themselves better with minor alterations in environmental stresses under proper psychiatric guidance. On the other hand, an abnormal tracing in such children indicates a degree of cerebral immaturity incommensurate with the chronological age reached, and therefore a child less likely to respond to minor variations in his milieu. An effort should immediately be made to place him in

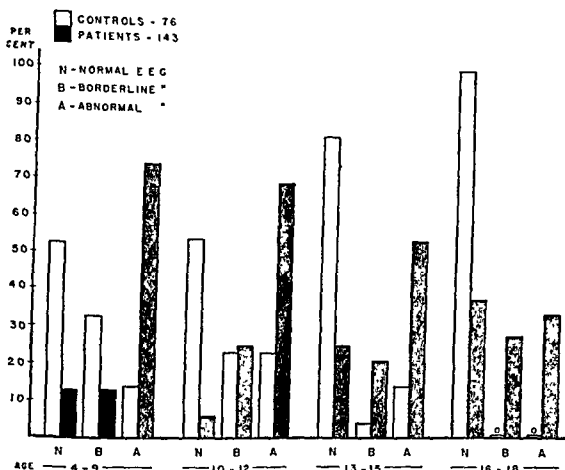


FIGURE 4. Percentage Distribution of Normal, Immature-Borderline and Immature-Abnormal Electroencephalographic Tracings (Patients and Controls) in Each Age Group.

*There is a greater percentage of abnormal tracings in the behavior disorders in each group than in the controls. The diagram also illustrates that with increase in age there is a diminution in the percentage of immature-abnormal tracings in the children with behavior disorders.*

is consistent for a normal record of that age range may be due to a delay in the normal development of the cerebrum. A further evidence of immaturity in these cases was the frequent occurrence of neurotic traits, such as enuresis, thumb sucking and nail biting. The tracing is a measure of the delayed development of the cerebrum; because of this delay in development, these patients do not make a satisfactory adjustment either to their environment or to the impact of puberty—46 per cent of the cases were between the ages of thirteen and fifteen. The fact that only 17 patients had siblings who were behavior problems, although subjected to the same environment, suggests that the environment is only a precipitating factor.

We believe that the electroencephalograph may become a useful adjunct in guiding therapeutic approach. For example, behavior-problem children with normal tracings might be expected

an environment modified to suit his limitations until he has achieved sufficient maturity.

## SUMMARY

The electroencephalograms of 143 children presenting behavior disorders are compared with those of a group of 76 normal controls of the same age range. The former had a higher percentage of immature-abnormal tracings and were more vulnerable to hyperventilation than the latter.

The patients and controls were divided into age groups: four to nine, ten to twelve, thirteen to fifteen and sixteen to eighteen. The patients with behavior disorders in each age group had a higher percentage of immature-abnormal tracings than the controls. Moreover, the records of the behavior disorders, comparing age group with age group, showed a progressive increase in normal records and a diminution in immature-abnormal records



with increase in age (from 74 per cent in the group from four to nine to 34 per cent in that from sixteen to eighteen). The possibility that the decrease in immature-abnormal records in the older age group was related to the maturation of the cerebrum is discussed.

### REFERENCES

1. Smith, J. R. The "occipital" and "precentral" alpha rhythms during the first two years. *J. Psychol.* 7:223-226, 1939.
2. Lindsley, D. B. Electrical potentials of the brain in children and adults. *J. Gen. Psychol.* 19:285-306, 1938.

3. Smith, J. R. The frequency growth of the human alpha rhythms during normal infancy and childhood. *J. Psychol.* 11:177-198, 1941.
4. Jasper, H. H., Solomon, P., and Bradley, C. Electroencephalographic analyses of behavior problem children. *Am. J. Psychiat.* 95:641-653, 1938.
5. Strauss, H., Rahm, W. E., and Barrera, S. E. Studies on a group of children with psychiatric disorders. I. Electroencephalographic studies. *Psychosom. Med.* 2:34-42, 1940.
6. Lindsley, D. B., and Cutts, K. K. Electroencephalograms of "constitutionally inferior" and behavior problem children: comparison with those of normal children and adults. *Arch. Neurol. & Psychiat.* 44:1199-1212, 1940.
7. Glueck, S., and Glueck, E. *Juvenile Delinquents Grown Up.* 330 pp. New York: Commonwealth Fund, 1940.
8. Gibbs, F. A., and Gibbs, E. L. *Atlas of Electroencephalography.* 221 pp. Cambridge: Privately printed, 1941.
9. Davis, H., and Wallace, W. McL. Electroencephalographic and subjective changes produced by standardized hyperventilation. *Tr. Am. Neurol. A.* 67:139-143, 1941.

## MEDICAL PROGRESS

### ARTIFICIAL RADIOACTIVE ISOTOPES IN MEDICINE AND BIOLOGY\*

JOSEPH F. ROSS, M.D.†

BOSTON

THE application of the isotopic tracer technique to medical investigation ranks in importance with the invention of the microscope and the discovery of the x-ray. During the relatively few years that isotopes have been employed in biologic research, they have contributed to fundamental discoveries in intermediary metabolism, and have provided new and promising forms of therapy for otherwise hopeless diseases.

The chief and unique value of isotopic tracers lies in their applicability to the study of normal metabolic processes in undisturbed organisms in functional, nutritional and energetic equilibrium. Previous methods of metabolic study, which relied on chemical technics, were of necessity concerned with the determination of accumulations of unnatural intermediate or end products, and frequently utilized observations made on sick or deranged organisms. However, with the use of isotopic tracers, the ebb and flow and interchange of normal foodstuffs, intermediate metabolic products, vitamins and even hormones can be followed in intact, living organisms.

Briefly, isotopes are atoms with identical chemical and biologic properties (since their nuclear charges and atomic numbers are the same), and are distinguished only by differences in atomic weight. Some isotopes are stable,—that is, they never change,—whereas others are radioactive and sooner or later undergo nuclear changes with the emission of radiations (gamma rays, beta rays or alpha particles). The stable isotopes, because of

the differences in their atomic weights, can be separated and detected quantitatively with the mass spectrometer, and the radioactive isotopes can be followed with an electroscope or a Geiger-Müller counter (instruments capable of detecting radiations). Since the organism does not distinguish between labeled and ordinary isotopes of the same element, biologic reactions in which the tracer isotope participates are identical with those occurring simultaneously with ordinary isotopes.<sup>1-3</sup> By the use of appropriate technics of detection, both stable and radioactive isotopes can therefore be employed in biologic research as marked or labeled atoms that serve to indicate the paths and reactions of their ordinary fellow atoms. It must be emphasized that the atoms of radioactive isotopes, except for slight differences in atomic weight, are indistinguishable from other atoms of the same element until they instantaneously give off their radiation. The amounts of radiation liberated by the minute "tracer doses" employed in biologic investigations are so small that they produce no alteration in normal physiologic processes, and it is only when large "therapeutic doses" are administered that radiation effects are produced.

The application of the isotopic tracer technique to biology is actually very simple. A substance—for example, an amino acid or a simple inorganic compound such as sodium phosphate—containing either stable or radioactive tracer atoms is fed to an animal or human subject, and subsequently the blood, tissues or secretions are tested for the presence of the labeled atoms. The presence of such atoms in any particular tissue indicates that some of the ingested material has been deposited in that tissue. In this fashion, the fate of the particular molecules of the amino acid or sodium phosphat

Reprints of articles in this series are not available for distribution, but the articles will be published in book form. The current volume is *Medical Progress: Annual, 1940* (Springfield, Illinois: Charles C Thomas Company, 1941. \$4.00).

\*From the Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine.

†Instructor in medicine, Boston University School of Medicine; associate, Robert Dawson Evans Memorial, Massachusetts Memorial Hospitals.

that were fed to the experimental subject can be distinguished from the fate of similar but unlabeled molecules of amino acid or sodium phosphate already present in the body. For example, by injecting sodium bicarbonate labeled with radioactive carbon and subsequently demonstrating the presence of this radioactive carbon in glycogen from the liver, Conant and his associates<sup>4</sup> were able to show that the animal organism can utilize carbon dioxide for the synthesis of glycogen. This truly revolutionary discovery could have been accomplished only by the use of a technic that allowed distinction between carbon atoms in the injected sodium bicarbonate and the carbon atoms of the complex carbohydrates already present in the body.

As early as 1923, Hevesy,<sup>5</sup> using the naturally occurring radioactive isotope of lead (radium D), studied the circulation of lead in plants, and similar technics were later applied to bismuth. Naturally occurring radioactive isotopes are few in number, however, and therefore the radioactive tracer technic could not be extensively applied to biologic investigation. The discovery by Joliot and Curie<sup>6</sup> that atoms could be made radioactive by artificial means, and the invention and development of the cyclotron by Lawrence and Cooksey,<sup>7</sup> made possible the production of artificially radioactive isotopes of practically all the elements, and during the last six years, many of these radioactive substances have been employed in biologic investigation. As medical investigators become familiar with the possibilities of this technic, and as more strongly radioactive substances are prepared and the methods of detection are made more sensitive, the use of isotopic tracers will undoubtedly be greatly expanded and will allow approach to many problems hitherto impossible of solution.

Although the only essential difference between the stable and radioactive isotopic tracer technics lies in the method of detection, this report is limited to a discussion of the radioactive tracers. An excellent review of the biologic applications of the stable isotopes has recently been prepared by Schoenheimer and Rittenberg.<sup>8</sup>

The extensive applications of radioactive tracers to studies of plant<sup>9</sup> and insect<sup>10</sup> physiology are beyond the scope of this paper, which is intended primarily to summarize only the more significant contributions with direct bearing on medical science.

Complete reviews of radioactive technics and of their varied applications have been prepared by Evans,<sup>11</sup> Greenberg,<sup>12</sup> Hamilton,<sup>13</sup> Hevesy<sup>14</sup> and Lawrence.<sup>15</sup>

## PHOSPHORUS

Radioactive phosphorus was the first of the isotopes to be applied to investigations of animal metabolism, and was used by Hevesy and his associates<sup>14, 16</sup> to study the absorption and distribution of phosphorus in rats, and to trace the formation of phospholipids and other phosphorus-containing organic substances in various tissues. During the seven years since this work was reported, over a hundred papers have appeared dealing with the application of this technic to studies of phosphorus metabolism. It was found that inorganic phosphates were readily absorbed from the upper intestinal canal, and were quickly converted into organic phosphorus compounds.<sup>17-19</sup> Phospholipids were synthesized most rapidly in the liver, kidney and intestinal wall and more slowly in other organs and tissues.<sup>20</sup> Phospholipid synthesis was apparently carried on in each tissue independently of similar activity in other organs,<sup>21</sup> and continued in tissue slices *in vitro*.<sup>22</sup> The rate of phospholipid turnover was definitely influenced by the level of lipids in the circulating blood, being accelerated when fats were absorbed from the intestine.<sup>21</sup>

Various footstuffs greatly influence the deposition of fat in the liver, and considerable interest has arisen concerning the role that these substances play in preventing or producing liver disease. The mode of action of such substances has been studied with the use of radioactive phosphorus as an indicator of phospholipid formation. It was found that the increase in liver fat produced by the feeding of cholesterol was associated with a decrease in the rate of formation of new phospholipid, although the total phospholipid content of the liver was not changed.<sup>23</sup> Choline, cystine and methionine (lipotropic substances) produced an opposite effect,—that is, a decrease in total liver fat and an acceleration in turnover of phospholipid,<sup>24-26</sup>—whereas other amino acids had no such effect.<sup>27</sup> It thus appears that the substances controlling deposition of lipids in the liver exert their effect by influencing phospholipid turnover.

The major portion of any given dose of radioactive phosphorus is eventually deposited in the bones.<sup>28, 29</sup> Therefore, the structures in close proximity to bone, such as the marrow, are subjected to localized bombardment by the beta rays given off by the decaying isotope. The first observations of the effect of such radiation were made by Scott and Cook,<sup>30</sup> who fed large doses of radioactive phosphorus to chicks and found a subsequent decrease in the number of circulating leukocytes. This observation suggested that radioactive phosphorus might be a valuable therapeutic agent in diseases in which there was abnormal

growth of leukocytes, such as leukemia. Lawrence and Scott<sup>31</sup> and Lawrence, Tuttle, Scott and Connor<sup>32</sup> investigated the effect of radioactive phosphorus on mice with leukemia, and found that it decreased the number of abnormal leukocytes in the circulating blood, and that the uptake of radioactive material by leukemic lymph nodes and spleens was three times greater than the uptake by normal lymph nodes and spleens. Subsequent studies showed that the rapid assimilation of radioactive phosphorus by tumor tissue was merely a reflection of its rapid metabolism, and was not a peculiarity of the tumor tissue itself.<sup>33-40</sup> However, the concentration of the radioactive material in neoplastic tissue subjected it to localized, *in situ* radiation, with resultant selective destruction of tumor cells, and explained the beneficial effect of radioactive phosphorus on animals with experimental leukemia.

These findings led to the therapeutic administration of radioactive phosphorus to human beings with leukemia, and in general the results were similar to those observed in animals with experimental leukemia. Patients with leukemia and polycythemia retained more radioactive phosphorus than normal persons, and it was concentrated in tumor tissues, leukemic leukocytes and leukemic bone marrow,<sup>41-43</sup> where it was built into nucleoproteins and phospholipids.<sup>39, 40</sup> The leukemic cells in the bone marrow, lymph nodes and peripheral blood were thus subjected to fairly specifically localized and intense radiation.

Erf, Tuttle and Lawrence,<sup>44</sup> who have recently summarized their clinical experiences with radioactive phosphorus in 100 cases of leukemia, believe that this form of therapy has distinct advantages over x-radiation because of the ease with which it can be administered (either by mouth or by intravenous injection), and because of the freedom from subsequent radiation sickness and skin reactions. They observed no clinical improvement in the patients with acute leukemia who were treated, although Warren<sup>45</sup> reported definite improvement in certain patients with acute leukemia treated with intravenously administered radioactive phosphorus. The results in chronic leukemia were more encouraging<sup>44</sup>: of 63 patients treated with radioactive phosphorus, 19 showed clinical improvement lasting from three to twelve months, 6 were completely well with normal laboratory findings for periods ranging from three months to two and a half years, and 2 were apparently completely cured and still living after two years. Investigators<sup>46</sup> at the Memorial Hospital in New York also found radioactive phosphorus a good and reliable therapeutic agent for lymphosarcoma and for chronic myelogenous and lymphatic leukemia, although it proved of little benefit in acute leukemia and in various other neoplastic diseases.

The natural history of leukemia, with its frequent remissions and exacerbations, necessitates extreme caution in evaluating the results obtained from any form of therapy, and since radioactive phosphorus has been used extensively for the treatment of leukemia for only two years, it is hazardous to draw too sweeping conclusions regarding its actual advantage over other forms of radiation therapy. Careful review of the reported cases indicates that the end results were little different from those that would have been obtained with x-radiation.

Six patients with polycythemia vera have been treated with radioactive phosphorus.<sup>47</sup> Considerable clinical improvement was noted, and there was some reduction in the erythrocyte count and hemoglobin level. The benefits obtained do not appear to have been superior to those that could have been achieved with the much less expensive and simpler procedures of restricting iron intake and performing phlebotomies.

All in all, radioactive phosphorus therapy appears to be a convenient but expensive method of administering radiation therapy to patients with leukemia and polycythemia. The results obtained are at least as good as those to be expected from x-ray treatment, and the technic definitely merits further investigation.

### IRON

For many years, there has been considerable controversy concerning the absorption and excretion of iron, and the most favorable form of the element for therapeutic use. Since it was impossible chemically to distinguish between iron that passed through the intestinal canal unabsorbed and iron that might have been excreted into the intestine, some investigators claimed that large quantities were absorbed and re-excreted, whereas others found that absorption did not take place in normal persons. With the use of radioactive iron, this problem has been solved, since the exact fate of a particular dose of iron can be determined accurately. Hahn and his collaborators<sup>48</sup> applied the radioactive tracer technic to the study of iron metabolism in dogs, and found that normal and plethoric animals absorbed very little iron, and that anemic animals assimilated considerable quantities. Moreover, iron absorption was controlled by the state of iron reserves in the body and not by the anemia *per se*, since animals made acutely anemic absorbed no more iron than they did when their blood levels were normal, and it was only after depletion of the iron stores in the tissues that iron was taken up from the bowel.<sup>49</sup>

Ross and Chapin<sup>50</sup> found that normal human subjects absorbed very small amounts of iron, although patients with the hypochromic anemia of

iron deficiency took up much larger amounts. Patients with untreated pernicious anemia, a condition in which the iron reserves of the body are adequate in spite of marked anemia, absorbed no more iron than normal subjects. However, the same patients took up considerable quantities of iron after treatment with liver extract and after depletion of body reserves of iron, even though the anemia had been relieved and was of minimal degree. The ferric, ferrous and reduced forms of iron were absorbed and utilized for hemoglobin formation with equal rapidity and facility.<sup>51, 52</sup> Insignificant amounts of iron were excreted in the urine and bile, and only minute amounts were eliminated in the feces under normal conditions, several years being required to excrete a surplus of iron equivalent to the total iron content of circulating hemoglobin.<sup>53</sup> These studies indicate that human subjects and experimental animals control iron metabolism by regulating the amounts of iron absorbed and not, as was formerly believed, by varying the amount excreted. In some way as yet unexplained, iron absorption occurs only when the reserves of tissue iron are depleted.

After absorption, radioactive iron is incorporated into the hemoglobin molecule with extreme rapidity, and is released into the circulation in newly formed erythrocytes within a few hours after ingestion.<sup>51, 54</sup> Once built into the hemoglobin molecule, radioactive iron is "fixed" within the erythrocytes,<sup>55</sup> and has provided a new method for studying cell and blood volume, since the total volume of blood or cells can be calculated from the degree of dilution of a known number of tagged cells injected into the vascular system of experimental subjects. With the use of cells labeled in this way, it has been found that the total volume of cells in the vascular system is less than was formerly supposed, and that very few if any cells are immobilized in the spleen or elsewhere in the body.<sup>56, 57</sup> The concept that the spleen serves as a reservoir for erythrocytes that can be mobilized in times of stress is thus subjected to serious doubt, and the increase in hematocrit produced by administration of adrenalin is probably caused by a redistribution of cells and plasma in the vascular system.

Further application of the radioactive tracer technic should clarify many problems of hemoglobin and iron metabolism, and the use of erythrocytes tagged with radioactive iron may be of considerable value in studying the changes in blood volume that occur in shock, cardiac failure and pregnancy.

#### IODINE

By means of radioactive iodine, it has been possible to follow the uptake of iodine by the thyroid gland, and to detect differences in iodine

metabolism in various types of thyroid disease.<sup>58</sup> When a suitably designed radiation detector was placed over the thyroid gland, and the patient then fed radioactive iodine, the rate of deposition of the radioactive material in the thyroid was registered on the counter. Normal subjects took up an amount of iodine approximately equivalent to that already present in the gland, and a maximum concentration was reached in about two days. This concentration was then maintained at a fairly constant level for the ensuing thirty days. In marked contrast to the normal glands, hyperactive glands of patients with Graves's disease assimilated four or five times more iodine, and took it up at an extremely rapid rate, the maximum concentration being reached in approximately four hours. The rapid uptake was followed by a rapid loss of iodine during the next few hours; this fact indicated that the mechanism by which the hyperactive gland stored iodine was much different from that of normal glands. Nontoxic goiters took up larger quantities of iodine than normal glands, but the rates of uptake and storage were very similar; iodine metabolism in nontoxic goiter was accordingly not significantly different from that of the normal gland. Atrophic glands of patients with myxedema took up only very minute quantities of iodine. Very recently, Hertz and Roberts<sup>59</sup> have employed the differential rates of iodine uptake by thyroid glands to distinguish between two types of hyperthyroidism that they classify as "ophthalmopathic" and "classic" Graves's disease.

Pretreatment with iodine markedly decreased the subsequent uptake of iodine by both normal and hyperactive glands.<sup>60-62</sup> This information has been applied clinically with the discovery that a single large dose of iodine produces the same therapeutic effect in Graves's disease as repeated massive iodination.<sup>61</sup> This suggests that the common clinical practice of administering Lugol's solution to patients with Graves's disease for weeks prior to thyroidectomy is unnecessary, a single large dose probably being about as effective.

The exact sites of localization of iodine in thyroid tissue can be determined by the unique technic of "radio autography." When thin sections of thyroid tissue containing radioactive iodine (removed from patients previously fed radioactive iodine) are placed on sensitive photographic plates, the beta rays liberated by the iodine expose the plate, the heaviest exposure being produced in regions in which the radioactive iodine is most concentrated. If these tissue sections are then stained and examined histologically, the areas of exposure on the photographic plate can be identified with the corresponding areas in the tissue, and the exact site of localization of the iodine easily determined.<sup>63</sup> Such studies show that iodine

is deposited in equal concentrations in the colloid and cells of active glands. However, carcinomatous thyroid tissue does not take up iodine. It is thus impossible to administer therapeutic radiation to this neoplastic tissue *in situ*, in the way that radiation can be given to leukemic tissue with radioactive phosphorus. On the other hand, since radioactive iodine does localize in hyperplastic thyroid tissue, Hertz and his associates<sup>60</sup> are employing radioactive iodine therapeutically in patients with Graves's disease. Considerable amounts of radiation can be administered *in situ* in this way, and it is hoped that this radiation will serve to inhibit the overactivity of the parenchymal cells, and thus reduce the overproduction of thyroid hormone.

#### SODIUM AND POTASSIUM

Radioactive sodium and potassium have been used extensively in the study of the permeability of various cell membranes to cations, and the essential extracellular nature of sodium and the intracellular character of potassium have been verified. Radioactive sodium entered the intracellular phase of sodium-containing tissues in proportion to the sodium content of the tissue—an indication that the cell membranes of such tissues are not completely impermeable to sodium.<sup>64</sup> Erythrocytes are permeable to both potassium and sodium ions,<sup>64-68</sup> and the classic theory of cation impermeability of the erythrocyte must therefore be considered as relative only. The cell membrane is undoubtedly more permeable to anions than it is to cations, but cations do penetrate it, and the difference in concentrations of cations inside and outside the cell must be due to some mechanism other than mere membrane impermeability.

Zwaardemaker<sup>69</sup> advanced the theory that the physiologic activity of some elements might be due to their natural radioactivity, and suggested that the intrinsic rhythmicity of the heart beat might be caused by the radiations given off by the naturally occurring isotope of potassium. He believed that the cessation of the heart beat produced by removal of potassium from perfusing fluid was due to the removal of these radiations. Glazko and Greenberg<sup>70</sup> effectively disproved this theory by replacing the potassium of perfusing fluid with radioactive sodium, which supplied infinitely more radiations than the naturally occurring radioactive potassium but which did not maintain cardiac rhythmicity. Various radioactive substances produced no immediate physiologic changes, even when the amount of radioactivity administered was very large.<sup>71</sup>

The possibility that neoplastic disease is caused by the concentration of naturally occurring radioactive potassium in tissue has been investigated by Lasnitzki,<sup>72</sup> who found that radioactive potassium was present in identical concentration in all

tissues studied, both normal and neoplastic. The same investigator<sup>73</sup> has recently reported, however, that the light, stable isotope of potassium ( $K^{39}$ ) is concentrated in tumor tissue, and in normal muscle tissue of tumor-bearing animals.

Since sodium is essentially extracellular in distribution, a method of determining extracellular fluid volume with radioactive sodium has been developed.<sup>74</sup> By this procedure, the average extracellular volume of human subjects was found to be 17.7 liters, or 23.5 per cent of the body volume. Approximately 85 per cent of this fluid was extravascular, and 15 per cent intravascular. Because of technical difficulties, this method is not so practical as the simpler thiocyanate one in general use.

#### CALCIUM AND STRONTIUM

Calcium and strontium are members of the same group in the periodic table of elements, and Pecher<sup>75, 76</sup> has found that radioactive calcium and radioactive strontium are distributed and metabolized in the animal organism in a similar fashion. Both are deposited in the skeleton, particularly in trabecular bone, epiphyses and regions of active skeletal growth.<sup>77</sup> The beta rays given off by radioactive calcium are too weak to be of value therapeutically, but the energetic beta particles emitted by radioactive strontium are capable of producing considerable tissue ionization, and should be of definite value in destroying neoplastic tissue. Consequently, since radioactive strontium is deposited in the newly formed osseous tissue of bone tumors, it is being used in the treatment of osteogenic sarcoma with the hope that radiation liberated *in situ* will be more effective than external x-radiation.<sup>75</sup>

#### CARBON

The carbon dioxide formed by the metabolism of the animal organism has been considered a waste product, and the animal organism was believed to be entirely dependent on the plant kingdom for conversion of inorganic carbon to organic forms suitable for foodstuffs. The recent work of Conant, Hastings and their associates<sup>4, 78</sup> indicates that this concept must be revised, and that the animal organism can use inorganic carbon dioxide for the formation of carbohydrates. Lactic acid containing radioactive carbon was fed to starved rats, and after two and a half hours, glycogen was isolated from the liver and assayed for its content of radioactive carbon. Although the amount of glycogen formed corresponded to 30 per cent of the lactate administered, only 1.6 per cent of the administered radioactive carbon was found in this newly formed glycogen; this indicates that the carbon used for synthesizing this glycogen did not originate directly or solely from the lactic acid molecule. This carbon must therefore have been

derived from some endogenous source, probably carbon dioxide. Subsequently, by injection of sodium bicarbonate containing radioactive carbon into starved rats, it was found that considerable amounts of the labeled carbon from the bicarbonate had been deposited in the liver as glycogen. It thus appears that the carbon dioxide liberated by carbohydrate catabolism is not entirely a waste product, but can be reutilized in the liver for formation of new glycogen.

### SULFUR

Sulfur compounds play a very significant role in numerous oxidation-reduction reactions in the body, and the essential nature of methionine, cystine and thiamin is well established. However, the intermediary metabolic reactions of these substances and their eventual fate in the body are still obscure. Using radioactive sulfur as a label, several investigators have studied the reactions of these substances in the body. Ingested inorganic sulfur apparently exchanged with the sulfur of the tissues to some extent, since its complete excretion was delayed.<sup>79</sup> It was not incorporated into cystine, however, and the sulfur of cystine did not exchange with inorganic sulfur.<sup>80, 81</sup> Thiamin (vitamin B<sub>1</sub>) containing radioactive sulfur was rapidly destroyed by both normal and thiamin-deficient human subjects.<sup>81</sup> Approximately 10 per cent of the body's content of vitamin B<sub>1</sub> was broken down every twenty-four hours.<sup>83</sup> When thiamin was injected into subjects maintained on a normal diet, there was a very large wastage, 61 per cent appearing in the urine and 11 per cent in the feces within a few hours.<sup>82, 83</sup> These findings indicate the probable futility of attempting to increase the body's stores of thiamin above the normal level.

### COBALT, COPPER, MANGANESE AND ZINC

Minute amounts of cobalt, copper, manganese and zinc are essential for the normal health and nutrition of animal organisms, but little is known of the exact roles that they play in metabolic processes. The radioactive isotopes of all these elements are easily prepared and detected, and afford an entirely new method of investigating their biologic activities. At present, they have been employed only for the study of absorption and excretion in animals,<sup>84-86</sup> but it is probable that they may soon be used in investigations of various essential enzyme systems.

### ARSENIC

Arsenical compounds are valuable therapeutic agents in syphilis and in various parasitic infections, although little is known of their distribution or mode of action. With the intention of

termining their action in these diseases, several investigators<sup>87, 88</sup> have made careful preliminary studies of the distribution of such compounds in various animals. Soon after injection, arsenic is concentrated in the liver, kidneys and lungs, but subsequently is so rapidly excreted in the urine that only minute amounts remain in the body after one week.

\* \* \*

Radioactive isotopes have been employed extensively as indicators of metabolic activity in experimental animals, and have been of greatest value in elucidating fundamental problems of normal physiology. The isotopic tracer technic has been applied to the study of disease in human beings only during the last three or four years, but already has resulted in significant improvement in the therapy of several metabolic and neoplastic diseases. Extension of the technic to other diseases will undoubtedly lead to a better understanding of underlying pathologic physiology and indicate new and better forms of treatment.

78 First Concord Street

### REFERENCES

1. Schenheimer R and Rittenberg D. Studies in protein metabolism. I. General considerations in the application of isotopes to the study of protein metabolism: the normal abundance of nitrogen isotopes in amino acids. *J Biol Chem* 127 285 290 1939.
2. Dole M P. Concentration of deuterium in organic compounds. II. A general discussion with particular reference to benzene. *J Am Chem Soc* 58 580-585 1936.
3. Dole M and Gibson R B. Deuterium abundance in organic compounds. III. Cholesterol. *J Am Chem Soc* 58 2552 2555 1936.
4. Conant J B, Cramer R D, Hastings A B, Klempner, F W, Solomon A K and Vennesland B. Metabolism of lactic acid containing radioactive carboxyl carbon. *J Biol Chem* 137 557 566 1941.
5. Hevesy G. The absorption and translocation of lead by plants: a contribution to the application of the method of radioactive indicators in the investigation of the change of substance in plants. *Biochem J* 17 439 445 1923.
6. Joliot F and Curie J. Artificial production of a new kind of radioelement. *Nature* 133 201 1934.
7. Lawrence E O and Cocksey D. On the apparatus for the multiple acceleration of light ions to high speeds. *Physical Rev* 50 1131 1140 1936.
8. Schoenheimer R and Rittenberg D. The study of intermediary metabolism of animals with the aid of isotopes. *Physiol Rev* 20 218 248 1940.
9. Stout P R and Hoagland D R. Upward and lateral movement of salt in certain plants as indicated by radioactive isotopes of potassium, sodium and phosphorus absorbed by roots. *Am J Botany* 26 320-324 1939.
10. Patton R L and Craig R. The rates of excretion of certain substances by the larvae of the mealworm *Tenebrio molitor* L. *J Exper Zool* 81 437 457, 1939.
11. Evans R D. Applied nuclear physics. *J Appl Phys* 12 260-279 1941.
12. Greenberg D M. Mineral metabolism: calcium, magnesium and phosphorus. *Ann Rev Biochem* 8 269 300 1939.
13. Hildreth J C. The applications of radioactive tracers to biology and medicine. *J Appl Phys* 12 440 460 1941.
14. Hevesy G. Application of radioactive indicators in biology. *Ann Rev Biochem* 9 641 667 1940.
15. Lawrence J H. Artificial radioactivity and neutron rays in biology and medicine. *Handbook of Physical Therapy*, Third edition, 537 pp. Chicago, American Medical Association 1938. Pp 438-455.
16. Chwifort O and Hevesy G. Radioactive indicators in the study of phosphorus metabolism in rats. *Nature* 136 754 1935.
17. Cohn W E and Greenberg D M. Studies in mineral metabolism with the aid of artificial radioactive isotopes. I. Absorption, distribution and excretion of phosphorus. *J Biol Chem* 123 185 198 1935.
18. Irf L A, Tuttle L W and Scott K G. Retention of orally administered radio phosphorus by mice. *Proc Soc Exper Biol & Med* 45 652 657, 1940.
19. Jones H B, Chalkoff I L and Lawrence J H. Phosphorus metabolism of the soft tissues of the normal mouse as indicated by radioactive phosphorus. *Am J Cancer* 40 235 242 1941.
20. Terleman I, Ruben S, and Chalkoff I L. Radioactive phosphorus as an indicator of phosphoryl and metabolism. I. The rate of formation and destruction of phospholipids in the fasting rat. *J Biol Chem* 122 169 182 1937.

21. Fries, B. A., Ruben, S., Perlman, I., and Chaikoff, I. L. Radioactive phosphorus as an indicator of phospholipid metabolism. II. The rôle of the stomach, small intestine and large intestine in phospholipid metabolism in the presence and absence of ingested fat. *J. Biol. Chem.* 123:587-593, 1938.
22. Fishler, M. C., Taugros, A., Perlman, I., and Chaikoff, I. L. Synthesis and breakdown of liver phospholipid in vitro with radioactive phosphorus as indicator. *J. Biol. Chem.* 141:809-818, 1941.
23. Perlman, I., and Chaikoff, I. L. Radioactive phosphorus as an indicator of phospholipid metabolism. VII. Influence of cholesterol upon phospholipid turnover in the liver. *J. Biol. Chem.* 128:735-743, 1939.
24. *Idem.* Radioactive phosphorus as an indicator of phospholipid metabolism. V. On the mechanism of the action of choline upon the liver of the fat fed rat. *J. Biol. Chem.* 127:211-220, 1939.
25. *Idem.* Radioactive phosphorus as an indicator of phospholipid metabolism. VIII. The influence of betaine on the phospholipid activity of the liver. *J. Biol. Chem.* 130:593-600, 1937.
26. Perlman, I., Stillman, N., and Chaikoff, I. L. Radioactive phosphorus as an indicator of phospholipid metabolism. XI. The influence of methionine, cystine, and cysteine upon phospholipid turnover in the liver. *J. Biol. Chem.* 133:651-659, 1940.
27. *Idem.* Radioactive phosphorus as an indicator of phospholipid metabolism. XII. Further observations on the effects of amino acids on phospholipid activity of the liver. *J. Biol. Chem.* 135:359-364, 1940.
28. Hevesy, G., Levi, H. B., and Rebbe, O. H. The rate of rejuvenation of the skeleton. *Biochem. J.* 34:532-537, 1940.
29. Hevesy, G. Application of isotopes in biology. *J. Chem. Soc.* 2:1213, 1939.
30. Scott, K. G., and Cook, S. F. The effect of radioactive phosphorus upon the blood of growing chicks. *Proc. Nat. Acad. Sc.* 13:265-272, 1937.
31. Lawrence, J. H. and Scott, K. G. Comparative metabolism of phosphorus in normal and lymphomatous animals. *Proc. Soc. Exper. Biol. & Med.* 40:694-696, 1939.
32. Lawrence, J. H., Tuttle, L. W., Scott, K. G. and Connor, C. L. Studies on neoplasms with the aid of radioactive phosphorus. I. The total phosphorus metabolism of normal and leukemic mice. *J. Clin. Investigation* 19:267-271, 1940.
33. Jones, H. B., Chaikoff, I. L., and Lawrence, J. H. Radioactive phosphorus as an indicator of phospholipid metabolism. VI. Phospholipid metabolism of neoplastic tissues (mammary carcinoma, lymphoma, lymphosarcoma, sarcoma 180). *J. Biol. Chem.* 128:631-644, 1939.
34. *Idem.* Radioactive phosphorus as an indicator of phospholipid metabolism. X. The phospholipid turnover of fraternal tumors. *J. Biol. Chem.* 133:319-327, 1940.
35. *Idem.* Phosphorus metabolism of neoplastic tissues (mammary carcinoma, lymphoma, lymphosarcoma) as indicated by radioactive phosphorus. *Am. J. Cancer* 40:243-250, 1940.
36. Kohman, T. P., and Rusch, H. P. Relative metabolic activities of normal and tumorous liver nucleoproteins indicated by radioactive phosphorus. *Proc. Soc. Exper. Biol. & Med.* 46:403, 1941.
37. Marshak, A. Uptake of radioactive phosphorus by nuclei of liver and tumors. *Science* 92:460, 1940.
38. Erf, L. A. Retention of radiophosphorus in whole and aliquot portions of tissues of a patient dead of leukemia. *Proc. Soc. Exper. Biol. & Med.* 47:287-289, 1941.
39. Tuttle, L. W., Erf, L. A., and Lawrence, J. H. Studies on neoplasms with the aid of radioactive phosphorus. II. The phosphorus metabolism of the nucleoprotein, phospholipid and acid soluble fractions of normal and leukemic mice. *J. Clin. Investigation* 20:57-61, 1941.
40. *Idem.* Studies on neoplasms with the aid of radioactive phosphorus. III. The phosphorus metabolism of the phospholipid, acid soluble and nucleoprotein fractions of various tissues of normal and leukemic mice following the administration of "tracer" and "therapeutic" doses of radio-phosphorus. *J. Clin. Investigation* 20:577-581, 1941.
41. Tuttle, L. W., Scott, K. G., and Lawrence, J. H. Phosphorus metabolism in leukemic blood. *Proc. Soc. Exper. Biol. & Med.* 41:20-25, 1939.
42. Erf, L. A., and Lawrence, J. H. Phosphorus metabolism in neoplastic tissue. *Proc. Soc. Exper. Biol. & Med.* 46:694, 1941.
43. *Idem.* Clinical studies with the aid of radioactive phosphorus. I. The absorption and distribution of radio-phosphorus in the blood and its excretion by normal individuals and patients with leukemia. *J. Clin. Investigation* 20:567-575, 1941.
44. Erf, L. A., Tuttle, L. W., and Lawrence, J. H. Clinical studies with the aid of radio-phosphorus. IV. The retention in blood, the excretion and the therapeutic effect of radio-phosphorus on patients with leukemia. *Ann. Int. Med.* 15:487-543, 1941.
45. Warren, S. The treatment of leukemia by radioactive phosphorus. *New Eng. J. Med.* 223:751-754, 1940.
46. Kenney, J. M. Radioactive phosphorus as a therapeutic agent in malignant neoplastic disease. *Cancer Research* 2:130-145, 1942.
47. Erf, L. A., and Lawrence, J. H. Clinical studies with the aid of radio-phosphorus. III. The absorption and distribution of radio-phosphorus in the blood of, its excretion by, and its therapeutic effect on patients with polycythemia. *Ann. Int. Med.* 15:276-290, 1941.
48. Hahn, P. F., Bale, W. F., Lawrence, E. O., and Whipple, G. H. Radioactive iron and its metabolism in anemia: its absorption, transportation and utilization. *J. Exper. Med.* 69:739-753, 1939.
49. Hahn, P. F., and Whipple, G. H. The use of radioactive iron in the study of problems of iron metabolism and experimental anemia. *J. Appl. Phys.* 12:23, 1941.
50. Ross, J. F., and Chapin, M. A. The selective absorption of radioactive iron by normal and iron-deficient human subjects. *J. Clin. Investigation* 20:437, 1941.
51. Hahn, P. F., Ross, J. F., Bale, W. F., and Whipple, G. H. The utilization of iron and the rapidity of hemoglobin formation in anemia due to blood loss. *J. Exper. Med.* 71:731-736, 1940.
52. Ross, J. F., and Chapin, M. A. Unpublished data.
53. Hahn, P. F., Bale, W. F., Hettig, R. A., Kamen, M. D., and Whipple, G. H. Radioactive iron and its excretion in urine, bile, and feces. *J. Exper. Med.* 70:443-451, 1939.
54. Miller, L. L., and Hahn, P. F. The appearance of radioactive iron as hemoglobin in the red cell: the significance of "easily split" iron. *J. Biol. Chem.* 134:585-590, 1940.
55. Hahn, P. F., Bale, W. F., Ross, J. F., Hettig, R. A., and Whipple, G. H. Radio-iron in plasma does not exchange with hemoglobin iron in red cells. *Science* 92:131, 1940.
56. Hahn, P. F., Balfour, W. M., Ross, J. F., Bale, W. F., and Whipple, G. H. Red cell volume circulating and total as determined by radio-iron. *Science* 93:87, 1941.
57. Hahn, P. F., Ross, J. F., Bale, W. F., Balfour, W. M., and Whipple, G. H. Red cell and plasma volumes (circulating and total) as determined by radio iron and by dye. *J. Exper. Med.* 75:221-232, 1942.
58. Hamilton, J. G., and Soley, M. H. Studies in iodine metabolism of the thyroid gland in situ by the use of radio-iodine in normal subjects and in patients with various types of goiter. *Am. J. Physiol.* 131:135-143, 1940.
59. Hertz, S., and Roberts, A. Radioactive iodine as an indicator in thyroid physiology. V. The use of radioactive iodine in the differential diagnosis of two types of Graves' disease. *J. Clin. Investigation* 21:31, 1942.
60. Hertz, S., Roberts, A., Means, J. H., and Evans, R. D. Radioactive iodine as an indicator in thyroid physiology: iodine collection in normal and hyperplastic thyroids in rabbits. *Am. J. Physiol.* 128:565-576, 1940.
61. Hertz, S. Radioactive iodine as an indicator in thyroid physiology: observations on rabbits and on goiter patients. *J. Appl. Phys.* 12:313, 1941.
62. Hertz, S., Roberts, A., and Salzer, W. T. Radioactive iodine as an indicator in thyroid physiology. IV. The metabolism of iodine in Graves' disease. *J. Clin. Investigation* 21:25-29, 1942.
63. Hamilton, J. G., Soley, M. H., and Eichorn, K. B. Deposition of radioactive iodine in human thyroid tissue. *Univ. California Publ., Pharmacol.* (No. 28) 1:339-367, 1940.
64. Manery, J. F., and Bale, W. F. The penetration of radioactive sodium and phosphorus into the extra- and intra-cellular phases of tissues. *Am. J. Physiol.* 132:215-231, 1941.
65. Cohn, W. E., and Cohn, E. T. Permeability of red corpuscles of the dog to sodium ion. *Proc. Soc. Exper. Biol. & Med.* 41:445-449, 1939.
66. Mullins, L. J., Fenn, W. O., Noonan, T. R., and Haegle, L. Permeability of erythrocytes to radioactive potassium. *Am. J. Physiol.* 135:93-101, 1941.
67. Noonan, T. R., Fenn, W. O., and Haegle, L. The distribution of injected radioactive potassium in rats. *Am. J. Physiol.* 132:474-483, 1941.
68. Fenn, W. O., Noonan, T. R., Mullins, L. J., and Haegle, L. The exchange of radioactive potassium with body potassium. *Am. J. Physiol.* 135:149-163, 1941.
69. Zwaardemaker, H. On physiological radio-activity. *J. Physiol.* 53:273-289, 1920.
70. Glazko, A. J., and Greenberg, D. M. Is the physiological activity of potassium due to its natural radioactivity? *Am. J. Physiol.* 125:405-409, 1939.
71. Hamilton, J. G., and Alles, G. A. The physiological action of natural and artificial radioactivity. *Am. J. Physiol.* 125:410-413, 1939.
72. Lasnitzki, A. On the radioactivity of potassium in tumour tissue. *Am. J. Cancer* 35:225-229, 1939.
73. Lasnitzki, A., and Brewer, A. K. Isotopic constitution of potassium in animal tumors and muscle from tumor-bearing animals. *Cancer Research* 1:776-778, 1941.
74. Kalreider, N. L., Meneely, G. R., Allen, J. R., and Bale, W. F. Determination of the volume of the extracellular fluid of the body with radioactive sodium. *J. Exper. Med.* 74:569-590, 1941.
75. Pecher, C. Biological investigations with radioactive calcium and strontium. I. Comparison of biologic activity. *Proc. Soc. Exper. Biol. & Med.* 46:86-91, 1941.
76. *Idem.* Biological investigations with radioactive calcium and radioactive strontium. *J. Appl. Phys.* 12:318, 1941.
77. Pecher, C., and Pecher, J. Radio-calcium and radio-strontium metabolism in pregnant mice. *Proc. Soc. Exper. Biol. & Med.* 46:91-94, 1941.
78. Hastings, A. B., and Kistiakowsky, G. B. Biological studies with radioactive carbon. *J. Appl. Physics* 12:322, 1941.
79. Borsook, H., Keighley, G., Yost, D. M., and McMillan, E. Urinary excretion of ingested radioactive sulfur. *Science* 86:525, 1937.
80. Tarver, H., and Schmidt, C. L. A. The conversion of methionine to cystine: experiments with radioactive sulfur ( $S^{35}$ ). *J. Biol. Chem.* 130:67-80, 1939.
81. *Idem.* The use of radioactive sulfur,  $S^{35}$ , for metabolic studies. *J. Appl. Phys.* 12:323, 1941.
82. Borsook, H., Hatcher, J. B., and Yost, D. M. The course of vitamin B<sub>1</sub> (thiamin) metabolism in man as indicated by the use of radioactive sulfur. *J. Appl. Phys.* 12:325, 1941.
83. Borsook, H., Buchman, E. R., Hatcher, J. B., Yost, D. M., and McMillan, E. Course of thiamin metabolism in man as indicated by use of radioactive sulfur. *Proc. Nat. Acad. Sc.* 29:412-418, 1940.
84. Schultze, M. O., and Simmons, S. J. Studies with radioactive copper. *J. Appl. Phys.* 12:315, 1941.
85. Greenberg, D. M., and Campbell, W. W. Studies in mineral metabolism with the aid of induced radioactive isotopes. IV. Manganese. *Proc. Nat. Acad. Sc.* 26:448-452, 1940.
86. Copp, D. H., and Greenberg, D. M. Studies in mineral metabolism with the aid of artificial radioactive isotopes. VI. Cobalt. *Proc. Nat. Acad. Sc.* 27:153-157, 1941.
87. Hunter, F. T., and Kip, A. F. The fate of inorganic arsenic in certain animals and man. *J. Appl. Phys.* 12:324, 1941.
88. du Pont, O., Ariel, I., and Warren, S. L. The distribution of radioactive arsenic in the normal and tumor-bearing (Brown-Pearce) rabbit. *Am. J. Syph., Gonorr. and Ven. Dis.* 26:96-118, 1942.

# CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTE-MORTEM AND POST-MORTEM RECORDS AS USED  
IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

CASE 28211

## PRESENTATION OF CASE

A sixty-three-year-old businessman was admitted to the hospital because of fever, cough, chest pain and sputum.

The patient had been in fair health except for "arthritis," some malnutrition and a chronic cough that was productive of about a cupful of sputum a day during the six months before entry. Two days before entry, following exposure to cold, he experienced a shaking chill followed by fever and pain in the front of the left chest; this was made worse by breathing. The sputum became tinged with blood.

The patient drank much alcohol until four years before entry and ate very poorly. The more remote history was not available.

Examination showed an acutely ill man, flushed and dyspneic with dusky cyanosis. There was dullness in the left midaxilla extending to the left base posteriorly, where breath sounds were diminished, with a suggestion of bronchovesicular breathing and rhonchi. There was a questionable friction rub. The heart seemed normal. The abdomen was very slightly distended.

The blood pressure was 130 systolic, 80 diastolic. The temperature was 99.5°F., the pulse 112, and the respirations 31.

Examination of the blood showed a red-cell count of 3,620,000 with 11.3 gm. hemoglobin, and a white-cell count of 18,000 with 90 per cent polymorphonuclears, 7 per cent lymphocytes and 3 per cent monocytes. The blood Hinton reaction was negative. The urine showed a +++ test for albumin, a specific gravity of 1.010 and a sediment containing numerous white blood cells with rare casts and red cells and no bacteria. A Type 9 pneumococcus was identified in the sputum by the Neufeld reaction.

Röntgenograms of the chest showed generalized increase in linear markings throughout the right lung field and in the upper portion of the left lung field. The lower part of the left lung field was homogeneously dense, and in the lateral view showed numerous areas of consolidation in the region of the left lower lobe. There was much calcification in the aorta.

The patient was treated with small doses of sulfadiazine and did fairly well for two days. The

temperature ranged from 98.6 to 100°F. The urine remained filled with white blood cells and albumin. On the third hospital day, there was gross hematuria, and the patient complained of pain in the left flank. No crystals were evident in the urine, and the sulfadiazine blood level had reached a maximum value of only 8 mg. per 100 cc. The nonprotein nitrogen was 56 mg. per 100 cc., rising to 75 mg. two days later. Intravenous glucose in physiologic saline solution was given in four clyses. On the fifth hospital day, there was complete dullness over the left lower lobe, with diminished breath sounds. The next day, extreme dyspnea appeared. The temperature spiked to 102°F. for one reading. Bubbling rales became audible in both lung fields. On the eighth day, the patient became cyanotic, and the systolic blood pressure dropped to about 100. The urinary output became less than 500 cc. per day, with a specific gravity of 1.006, a + test for albumin and many red cells and a few unidentified crystals in the sediment. The nonprotein nitrogen rose to 102 mg. per 100 cc. Cheyne-Stokes respirations appeared, and the patient expired the following day.

## DIFFERENTIAL DIAGNOSIS

DR. JOHN H. TALBOTT: This patient had an exudative respiratory disturbance for six months and an acute respiratory disease for two days. We have no further information about the "arthritis," the anemia or the cause of the malnutrition. He had been a heavy imbibor of alcoholic beverages. These facts are probably incidental to the malady responsible for death. The association of arthritis and kidney disease makes one raise the question of gout, but I think we can dismiss it without further consideration. There is no evidence that the patient had cirrhosis of the liver, which one might suspect on the basis of the alcoholic history. There are no data about urinary symptoms or other evidence to suggest a nephritis. The first evidence of kidney disease was observed on admission to the hospital; this was in addition to an acute pulmonary process. Nothing is stated about the examination of the fundi. We do not know whether there were any retinal changes, which are most important diagnostically in a consideration of a kidney lesion. I realize that a patient who comes in with pneumonia may have a very cursory examination of the eyegrounds. Was any statement made in the record about a retinitis?

DR. TRACY B. MALLORY: There is a check against "fundus" on the chart, which should mean that they were looked at and nothing found.

DR. TALBOTT: The patient had clinical signs of pneumonia and a white-cell count of 18,000. The



temperature was 99.5°F., the pulse 112, and the respirations 31.

I should like to see the x-ray films.

DR. MALLORY: The films were lost.

DR. TALBOTT: I was afraid something like that would happen, having hoped that we should get additional information, from the interpretation of the x-ray films, whether or not there was pulmonary edema such as might be seen in acute nephritis.

We must be content with what we are given in the record. The absence of clubbing of the fingers makes one disinclined to attribute too much significance to the chronic cough, such as might be associated with bronchiectasis or advanced pulmonary fibrosis. Undoubtedly, this patient had a chronic pulmonary process as well as an acute one. There was no history of exposure to tuberculosis, no examination of the sputum for tubercle bacilli, and no history of hemoptysis. I am inclined to make a diagnosis of chronic nontuberculous pulmonary infection, which was probably exaggerated by bronchitis in the six months before admission and was responsible for the expectoration of a cupful of sputum daily. The acute process was probably a pneumococcal pneumonia.

DR. MALLORY: The X-ray Department did call it pneumonia.

DR. TALBOTT: Now we come to the kidneys. It is stated that the patient had small doses of sulfadiazine, and yet the blood level rose to 8 mg. I think one can say that some renal impairment must have existed to give a blood level of 8 mg. on small doses of sulfadiazine. The onset of pain in the left flank, followed by hematuria and a rising nonprotein nitrogen, makes me believe that this patient had renal impairment secondary to sulfadiazine toxicity. Renal involvement following sulfadiazine ingestion is not so common as it is with some of the other sulfonamides. Two conditions may predispose to the development of a sulfadiazine reaction in the kidney: a patient may develop a sensitivity to the drug because of previous ingestion; and probably much more important clinically is the presence of a pre-existing renal disease. A patient who has a pre-existing renal disease is more prone to develop renal toxicity from any of the sulfonamides. The acute episode on the second day was, I believe, associated with sulfadiazine damage to the kidney, and I think we are going to find, if the kidney was prepared properly, plenty of evidence of sulfadiazine crystals microscopically.

So far as the mechanism of renal damage from sulfonamides is concerned, it is probably a combination of toxic damage to the parenchyma of

the kidney and plugging of the convoluted tubules by precipitated crystals. Patients who develop a sulfonamide reaction may have complete shutdown of one or both kidneys. The sulfadiazine reaction was treated with intravenous glucose and physiologic saline solution. I have no comments to make in this connection. I think the use of saline is undesirable in sulfonamide anuria. The solubility of sulfonamides is depressed in a urine of high salt content. If urination is resumed, the tendency to further precipitation is augmented. Moreover, intravenous saline solution may cause some edema of the tubules and delay restoration of function. I think a patient with a sulfadiazine reaction should probably get glucose and not saline solution. The question of alkalinity of body fluids, particularly urine, has been raised in connection with sulfadiazine reactions in the kidney. There is conflicting evidence in the literature concerning whether or not an alkaline urine is less harmful to a damaged kidney than an acid one. Indian evidence is based on renal damage from transfusion, in which the precipitation of hemoglobin or rather the damage from precipitation of hemoglobin, is less with an alkaline than with an acid urine. On the basis of this and other experimental evidence, I should have recommended either sodium bicarbonate by mouth or sodium lactate intravenously and continued alkalinization of the patient until most of the evidence of kidney damage had disappeared.

What is the prognosis in renal toxicity due to sulfadiazine? This patient died. If he had had an overwhelming malady, I do not believe that the kidney damage itself would have been fatal. Did he die of pneumonia alone? I do not believe so. I think it was a combination of renal disease and pneumonia. The renal disease was also a combination of sulfadiazine reaction superimposed on the pre-existing kidney disturbance.

What was the nature of this kidney disturbance which was manifested by a ++++ test for albumin on admission and a + test for albumin on one or two subsequent occasions? The patient had a specific gravity of 1.010 on admission; yet presumably was dehydrated. One can assume that any patient who has pneumonia is probably dehydrated by the time he comes to the hospital. The sediment contained many white cells, but red cells were noted until after the ingestion of sulfadiazine.

Was this an acute or a chronic nephritis? If it were the former, it might be associated with bronchitis. We have no evidence—from the physical grounds, from the blood pressure or from the history of kidney disease—whether or not

thing had been going on in the kidney before admission to the hospital. I do not believe I can go any farther in differentiating the primary renal lesions in this patient beyond affirming that there was something that predisposed to the sulfadiazine toxicity. In conclusion, I think we have two conditions in the lungs, and two in the kidneys. In the kidney, there was an underlying nephritis, with a superimposed sulfadiazine reaction.

DR. FLETCHER COLBY: Could not the left-sided renal pain with gross hematuria be explained in some other way than by a drug reaction—that is, by something such as a renal infarct? Gross hematuria and pain in a sulfadiazine reaction are unusual, it seems to me, especially when we do not find crystals in the urine. I do not remember any patients with gross hematuria from sulfadiazine, and I do not remember any who have had pain as the prominent symptom.

DR. TALBOTT: Do you think that the ureter was plugged on that side?

DR. COLBY: I do not know.

DR. CHAMP LYONS: I do not believe we know everything about the renal complications of sulfanilamide therapy. The kidney content of sulfanilamide and sulfadiazine is apparently a reflection of the blood concentration of the drugs, but sulfathiazole and sulfapyridine may be present in the kidney in concentrations above the blood content of sulfonamides. Two types of renal complications occur: one is a toxic effect on the tubules, and the other results from the precipitation of crystals of the free or conjugated drug; both produce hematuria. Sulfathiazole and sulfapyridine crystals may precipitate out and obstruct the kidney tubules, pelvis or ureters, but sulfadiazine crystals, in my experience, are limited to the pelvis and ureter—they do not precipitate in the kidney tubules. Hence, in sulfadiazine therapy, the presence of crystals and blood in the urine suggests ureteral obstruction by crystals. In this case of hematuria without crystalluria, I should consider the kidney lesion an acute toxic nephritis due to sulfadiazine or some other agent.

DR. TALBOTT: You think the pain might come from a toxic reaction rather than from the crystals? I had attributed it to the formation of crystals.

DR. LYONS: Left costovertebral pain and tenderness may occur without crystal formation. In painful crystalluria due to sulfadiazine, there is usually the flank pain of ureteral colic. I am here to see what Dr. Mallory is going to say about the kidneys, because I am puzzled about the clinical interpretation of hematuria in sulfonamide therapy.

DR. ALLAN M. BUTLER: I missed the rationale of the alkalization of this patient. Did Dr. Talbott

want to give him alkali to provide the maximum solubility for the hemoglobin or for the sulfadiazine in the urine or for some general reason because of the presence of renal damage?

DR. TALBOTT: The last two, in the presence of hematuria.

DR. BUTLER: If it is the last two, I should question the wisdom of alkali, because I do not believe we have very definite evidence that alkali within the pH range of urine changes to any appreciable degree the solubility of any known sulfadiazine derivatives.

DR. LYONS: Then you have not accepted Flippin's<sup>1</sup> results on the diminished incidence of crystalluria in patients receiving soda bicarbonate along with sulfonamides?

DR. BUTLER: For the reason that, if I remember the paper, he had no control of the urine volume. Is that the one he read at the meeting of the American College of Physicians last spring?

DR. LYONS: Yes.

DR. TALBOTT: According to reports in the literature,<sup>2,3</sup> the acidity of the urine is a most important factor. The solubility of a sulfonamide at pH 7.5 is nearly double that at pH 6.0. This fact should be appreciated by all who use the drugs, since alkalization of the urine is a simple and harmless procedure.

DR. BUTLER: The work of Sunderman and Pepper<sup>2</sup> indicates some increase in the solubility of sulfathiazole. The bulk of evidence shows no increase in that of sulfanilamide or sulfapyridine. So far as I know, there is no quantitative evidence for sulfadiazine.\*

DR. LYONS: I believe the clinical observation of decreased incidence of crystalluria is sufficient to make it likely that alkalization may increase the solubility of free sulfonamide crystals without affecting the conjugated sulfonamide derivatives.

DR. BUTLER: I agree that there is a possibility, because there is considerable evidence that there are derivatives of sulfonamides excreted in the urine whose identity has not been established; such derivatives may have an increased solubility with a pH of 7.8.

DR. LYONS: Do you agree that the present evidence warrants the alkalization of the patient? Is that unfair to assume?

DR. BUTLER: I am not sure. According to the third criterion, you apparently believe you are doing something to protect the injured kidney by alkali. Does anyone know whether that is so?

DR. TALBOTT: In a transfusion reaction, we are certain that alkali helps.

\*Dr. Butler reports that since this conference he has learned of unpublished work showing that the solubility of urinary sulfadiazine may increase as much as fivefold with an increase in urinary pH from 5.5 to 7.8. He has therefore requested that this information be added to this discussion since it suggests that urinary alkalization should specifically be beneficial with sulfadiazine therapy.

DR. BUTLER: There, one is dealing with the first criterion, when alkalization does make sense. But does it for the third purpose?

DR. MALLORY: The patient under discussion did not have hemoglobinuria but hematuria.

#### CLINICAL DIAGNOSES

Lobar pneumonia (Type 9 pneumococcus).

Nephritis.

Uremia.

#### DR. TALBOTT'S DIAGNOSES

Chronic nontuberculous pulmonary infection.

Pulmonary fibrosis.

Pneumococcal pneumonia, Type 9.

Sulfadiazine reaction.

Nephritis, ? acute or chronic.

#### ANATOMICAL DIAGNOSES

Lobar pneumonia.

Chronic pulmonary fibrosis, with emphysema.

Acute glomerular nephritis.

Arteriosclerosis, aortic and iliac.

#### PATHOLOGICAL DISCUSSION

DR. MALLORY: Autopsy showed evidence of old chronic pneumonitis, with extensive pulmonary emphysema and fibrosis. It also showed a lobar pneumonia in the left lower lobe and extensive fresher pneumonia scattered throughout the other lobes. The kidneys were a little large, weighing 400 gm. When the capsule was stripped backward, the surface puckered somewhat, indicating that the substance was slightly edematous. The capsule stripped very easily, disclosing surfaces that showed a few red flecks. Most careful examination of the pelves, of the ureters and of the substance of the pyramids and cortex under the dissecting microscope showed no crystals anywhere. Microscopic sections showed a very acute glomerulonephritis, but characteristic enough so that I have not the slightest doubt about the diagnosis and there is no evidence of tubular damage.

DR. TALBOTT: You found no microscopic evidence of sulfadiazine toxicity?

DR. MALLORY: I should doubt if the drug ever got through the glomeruli.

DR. BUTLER: Did the picture account for the number of white cells in the urine?

DR. MALLORY: Not too well; it accounted for the gross hematuria well enough, and pain in the back is not uncommon with an acute glomerulonephritis.

DR. BUTLER: Was there a good deal of what Addis<sup>4</sup> calls "degenerative changes"?

DR. MALLORY: Not much—the lesion was too acute. The average glomerulus contained thirty to fifty polymorphonuclears, whereas seven to

twelve is about the normal number. There was also definite, though early, proliferation of endothelial nuclei. I do not believe one can seriously question the diagnosis of glomerulonephritis.

DR. LYONS: Feinstone and his co-workers<sup>5</sup> reported only tubular nephritis from sulfadiazine. Is it possible that sulfadiazine could cause glomerular damage?

DR. MALLORY: I am reluctant to believe any chemical substance can cause glomerular nephritis. I would rather believe that the sulfonamide so altered the immune reactions of the body that the latter reacted to a pneumococcus as if it were a streptococcus.

DR. BUTLER: How sure are you that the preparations in which the kidney was fixed did not destroy the sulfadiazine crystals?

DR. MALLORY: We looked for crystals with the dissecting microscope in unfixed tissue.

DR. TALBOTT: There were no crystals in the sections?

DR. MALLORY: No; in other cases of sulfonamide nephrosis, we have had no difficulty finding the crystals, usually in large numbers in the pelvis and frequently in significant numbers in the renal parenchyma.

DR. TALBOTT: Do you routinely put them in absolute alcohol?

DR. MALLORY: We have had no luck in preserving crystals in sections with any fixative or embedding method.

DR. ALLEN G. BRAILEY: Is it not possible to get a double infection, streptococcal as well as pneumococcal?

DR. MALLORY: I suppose that is conceivable.

#### REFERENCES

1. Schwartz, L., Flippin, H. F., Reinhold, J. G., and Domm, A. H. The effect of alkali on crystalluria from sulfathiazole and sulfadiazine. *J. A. M. A.* 117:514, 1941.
2. Sunderman, F. W., and Pepper, D. S. Sulfathiazole in blood and urine. *Am. J. M. Sc.* 200:790-795, 1940.
3. Curtis, A. C., and Sobin, S. S. The solubility of acetylsulfapyridine and acetylsulfathiazole in the urine. *Ann. Int. Med.* 15:884-889, 1941.
4. Addis, T., and Oliver, J. *The Renal Lesion in Bright's Disease*. 628 pp. New York: Paul B. Hoeber, Inc., 1931.
5. Feinstone, W. H., Williams, R. D., Wolff, R. T., Huntington, E., and Crossley, M. L. Toxicity absorption and chemotherapeutic activity of 2-sulfanilamidopyrimidine (sulfadiazine). *Bull. Johns Hopkins Hosp.* 67:427-456, 1940.

#### CASE 28212

#### PRESENTATION OF CASE

A sixty-seven-year-old Portuguese-American fisherman was admitted to the hospital because of abdominal pain of several hours' duration.

The patient was essentially well until the night before entry, when he noted gradual onset of periumbilical pain, which rapidly became worse. The pain was sharp, severe and fairly steady, although it was worse when gurgling occurred in the abdomen. On the morning of entry, the pain subsided and shifted to the midline below the

umbilicus. The patient vomited once, regurgitating only food that he had eaten that morning. During the illness, he passed neither gas nor feces.

Twelve years before entry, he was operated on for "stomach ulcers" at a community hospital, following four days' study. Subsequently he had frequent attacks of gas pains in the upper abdomen, which were always relieved by the taking of food. These pains were similar to the one that brought him to the hospital except that this last attack was not relieved by food.

On admission, the patient appeared well developed but thin. He was groaning from pain. The abdomen was distended and tympanitic, with diffuse spasms of the muscles. Although the markings of loops of bowel were visible, there were only occasional bursts and tinkles of high-pitched, loud peristalsis. There was dullness in both flanks, which appeared to shift when the patient was lying on his side. No masses were palpable. Tenderness seemed to center in the left upper quadrant. Rectal examination demonstrated a bulging, soft, boggy posterior cul-de-sac, which was not tender. There were no feces or gas in the rectum. The heart and lungs seemed normal.

The blood pressure was 160 systolic, 90 diastolic. The temperature was 99.5°F., the pulse 88, and the respirations 20.

Examination of the blood showed a white-cell

a notable absence of spasm. Unless the peritoneum is involved by infection, spasm, at least of an involuntary nature, will not occur. We know that if one puts a balloon in the small bowel and distends it so that very severe peristaltic pain is initiated in normal human beings, there is absolutely no spasm whatever; the abdomen is soft and flaccid. However, it is possible for certain persons to react to pain by voluntary spasm, and I am rather inclined to think, because of the essentially normal temperature, blood count and other evidence that does not point to infection, that the spasm described was probably voluntary and not involuntary, and was simply a reaction of the patient to discomfort.

The pain was periumbilical in the beginning and shifted to the midline below the umbilicus. That may be of some significance and might possibly indicate that whatever was the cause of the obstruction had moved downward a little bit. Also, because the pain subsided after admission, the patient's condition may have improved temporarily, and the degree of distention within the intestine may have become less. What relation this obstruction had to the previous history of operation for ulcers is problematical; since no details are given concerning the previous operation, it is perhaps not worth while for me to speculate about, except to say that gastric ulcers may become malignant and that the patient might have developed peritoneal metastases, although

be the cause of repeated attacks of small-bowel pain culminating in obstruction such as this. Cancer of the small bowel, carcinoma, sarcoma and lymphoma are quite rare but might be present.

Other possible causes that might be mentioned are changes in the circulation—an embolus, for example, since the patient is in the arteriosclerotic age, or mesenteric thrombosis. These usually are a little more severe and intense and more sudden in origin and are usually accompanied by a higher white-cell count than this man had and usually do not tend to improve once they have become well established. The nervous causes of intestinal obstruction are rare, but they are not unknown. We have recently had a patient who had such a small-bowel obstruction,—very possibly from a derangement of autonomic and vagus activity,—but ileus of that nature is usually secondary to a lesion elsewhere, such as one of the biliary or genitourinary tract.

It seems unlikely to me that this patient had pancreatitis, perforated ulcer, renal or biliary colic or a lesion of that sort. The symptoms are consistent with a diagnosis of middle or low small-bowel obstruction whose cause is not entirely clear, but I think, on the chances, one would have to put postoperative obstruction or obstruction due to an adhesive band as first choice.

DR. ARTHUR W. ALLEN: We connected the acute small-bowel obstruction with the previous surgery. We knew that the patient had had some sort of operation on his stomach. We did not know what kind. Dr. Charles Mixter, Jr., made a very excellent effort to get the Miller-Abbott tube into the small bowel under the fluoroscope. It seemed to leave the stomach and go to the right for a certain distance, but no farther, and then bounce back into the stomach. Consequently, without waiting and struggling with it any more, we decided that we had better explore the patient, since our experience with Miller-Abbott tubes that fail to pass the pylorus readily in small-bowel obstruction has been very unfortunate. If we had waited until morning, I think we could not have rescued this man because we could not have decompressed the small intestine with the Miller-Abbott tube.

At operation, we found that a subtotal gastrectomy with an antecolic anastomosis had been done, but he did not have a loop of small bowel threaded through this as we had suspected. Why not, I do not know, because it makes a beautiful trap. Also, the jejunum had been anastomosed over the transverse colon, with a very short loop that may have accounted for some of the postoperative symptoms. We were able to thread the Miller-Abbott tube down through the anastomosis and the distal link of jejunum very nicely on the operating table, and by suction from above we

slowly decompressed the small bowel. The tube obviously had gone down into the proximal blind loop of jejunum during the manipulation prior to laparotomy.

At a point approximately 40 cm. from the ileocecal valve, we encountered a large bolus of material within the lumen of the bowel back of which this obstruction had taken place. At first, we thought it probably was a mass of worms, but it turned out to be the pulp, in four sections, of an entire orange. The patient had probably swallowed these sections one after another, but they had got together in a long elliptical mass, which had stuck in this spot. Through a small incision in the bowel, we extracted this foreign body and closed the bowel. The decompression being satisfactory with the Miller-Abbott tube on the table, we were quite happy about it. If we had not been able to decompress the bowel in this manner, we should have emptied it of its contents by other means. In intestinal obstruction of this duration, the patient rarely survives the toxic effects of such material. The risk of leaving it within the bowel is very great. I have tried to locate some of Dr. George Monks's<sup>1</sup> original tubes on which to thread the intestines under these conditions—I once had one of these tubes in my possession and regarded it as a relic. Dr. David Cheever,<sup>2</sup> a few years ago, revived and used such a method. Recently, Wangenstein<sup>3</sup> has called attention to the value of a similar maneuver.

Aside from a brief pulmonary complication, this man did very well.

A PHYSICIAN: Is it not true that foreign bodies will stop at that location?

DR. ALLEN: It is the narrowest portion of the ileum and is somewhere in the neighborhood of 40 cm. from the ileocecal valve. Why there, I do not know. That is also the common site of a Meckel's diverticulum. Does Dr. Mallory know whether this has anything to do with the narrowing of the bowel in this location?

DR. TRACY B. MALLORY: No.

DR. ALLEN: Anatomically, that is considered the narrowest area in the small bowel.

#### CLINICAL DIAGNOSIS

Intestinal obstruction.

#### DR. SMITHWICK'S DIAGNOSIS

Small-bowel obstruction due to adhesive band.

#### ANATOMICAL DIAGNOSIS

Small-bowel obstruction due to phytobezoar.

#### REFERENCES

1. Monks, G. H. Studies in the surgical anatomy of the small intestine and its mesentery. *Ann. Surg.* 42:543-569, 1905.
2. Cheever, D. Operative evacuation of the small intestine in paralytic stasis. *New Eng. J. Med.* 207:1125-1131, 1932.
3. Wangenstein, O. H. Unpublished data.

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established in 1828

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND  
PUBLISHED UNDER THE JURISDICTION OF THE  
COMMITTEE ON PUBLICATIONS

Official Organ of  
THE MASSACHUSETTS MEDICAL SOCIETY  
and  
THE NEW HAMPSHIRE MEDICAL SOCIETY

## EDITORIAL BOARD

Joseph Garland, M.D.	Stephen Rushmore, M.D.
William B. Reed, M.D.	Henry R. Viets, M.D.
George R. Minot, M.D.	Robert M. Green, M.D.
Frank H. Lacey, M.D.	Charles C. Lund, M.D.
Shields Warren, M.D.	John F. Fulton, M.D.
George L. Tobey, Jr., M.D.	A. Warren Stearns, M.D.
C. Guy Lane, M.D.	Dwight O. Hara, M.D.
William A. Rogers, M.D.	Chester S. Keefer, M.D.

## ASSOCIATE EDITORS

Thomas H. Lanman, M.D.	Donald Munro, M.D.
Henry Jackson, Jr., M.D.	

Walter P. Bowers, M.D., EDITOR EMERITUS

Robert N. Nye, M.D., MANAGING EDITOR

Clara D. Davies, ASSISTANT EDITOR

**SUBSCRIPTION TERMS:** \$6.00 per year in advance, postage paid, for the United States (medical students, \$3.50 per year), Canada, \$7.04 per year, foreign funds \$8.52 per year for all foreign countries belonging to the Postal Union.

**MATERIAL** for early publication should be received not later than noon on Friday.

**THE JOURNAL** does not hold itself responsible for statements made by any contributor.

**COMMUNICATIONS** should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston, Massachusetts.

## TREATMENT OF PNEUMONIA IN THE HOME

THE introduction of chemotherapy with the sulfonamide drugs has revolutionized many beliefs concerning the treatment of acute infectious diseases. Not only has the mortality from many infections been markedly reduced, but most of the laborious methods of treatment either have been rendered totally unnecessary or are now resorted to only infrequently.

The severely ill patient with pneumonia—tense, flushed, markedly dyspneic and cyanotic, enclosed in an oxygen tent and with a distended abdomen covered with poultices or stupes—was a common sight in any large medical ward throughout the

pneumonia season only a few years ago. It is now rare to find such a case for demonstration to students, even in large general hospitals. This change is due in part to the fact that the diagnosis of pneumonia is being made early in the course of the disease, but particularly to the institution of chemotherapy with effective sulfonamide drugs as soon as the existence of an acute pulmonary infection is suspected.

The use of the first sulfonamide drugs—sulfanilamide and later sulfapyridine—was accompanied by severe toxic effects that necessitated great vigilance and many special diagnostic and therapeutic procedures. For this reason, and because persistent and adequate treatment with the sulfonamides is essential for the best results, most physicians believed that it was only fair to themselves and to their patients that sulfonamide therapy should be carried out in hospitals, where adequate personnel and other facilities are more readily available for the management of problems as they arise.

As physicians acquired more experience in the use of the sulfonamide drugs and as new derivatives became available that were more effective and at the same time gave fewer reactions, the attitude toward hospitalization changed materially. The physician is now in a position to administer effective therapeutic doses of such drugs as sulfathiazole and sulfadiazine in the home and to carry out the essential observations with a minimum of effort.

Elsewhere in this issue of the *Journal*, there is a report on the treatment of 132 cases of pneumonia with sulfathiazole in the home. The patients were from among the poor residents of Boston who could not afford to pay for the services of private physicians. The success of this venture is indicated by the very low mortality—3.8 per cent—and by the rarity with which complications of either the disease or the treatment were encountered. The results are all the more remarkable since a large percentage of the patients were over fifty years old and some of them had positive blood cultures. These favorable results are due

in large measure to the early institution of treatment and to the diligence and interest of the physicians engaged in this work. Nevertheless, most of the procedures that these district physicians were called on to do could easily be carried out by any private practitioner. This excellent work has served to relieve, in some measure, the marked overcrowding of the public wards of Boston hospitals during the season when respiratory infections are prevalent.

Some degree of caution is still necessary, especially since all the newer drugs give rise to untoward reactions, particularly in the urinary tract. The practice of forcing fluids is to be stressed, particularly in patients treated with these drugs in the home, and special precautions should be taken with those who are suspected of having impaired renal function. Blood counts must be taken frequently in patients who require prolonged treatment (over periods lasting more than two weeks), to forestall the occurrence of agranulocytosis. The danger that the patient will not carry out the treatment or will discontinue it too soon is perhaps of greater consequence in the domiciliary management of severe infections like pneumonia. The success of sulfonamide treatment in this disease, as in most infections treated with these agents, depends on adequate and continuous treatment until a complete cure is effected.

The successful experiences of the Boston Dispensary physicians are not unique and are not dependent entirely on a highly trained "team." Physicians in private practice can obtain similar results. This is demonstrated in a recent report by McClure,\* who reviewed 386 cases of pneumonia treated by private practitioners in Ontario. Sulfapyridine alone was used in the treatment of 92 per cent of these cases, most of which were associated with type-specific pneumococci. It is of interest that the mortality in the cases treated with sulfapyridine was 3.7 per cent, which is almost identical with that reported in the patients treated in Boston with sulfathiazole. It is also worthy of note that the average total amount of sulfapyridine

used was only half as much as that of sulfathiazole. The difference may very well be related to the more frequent and severer nausea and vomiting that accompany sulfapyridine treatment and induce both patient and physician to discontinue treatment sooner than might otherwise be deemed necessary.

### A COMPLIMENT

Under the title, "*The New England Journal of Medicine*," the following editorial appeared in the April 15 issue of the *New York State Journal of Medicine*:

In a letter to the *New York Times* of March 25, 1941, Dr. Henry R. Viets of Boston, quoting an editor in that paper, of March 22, entitled "A Yale Genealogy says:

It would be interesting to trace the lives and usual early deaths of magazines that have taken the name of New England. . . . One stalwart in that line is the *New England Journal of Medicine*, the first journal of medicine in this country, if not in the world, which has continued, despite changes in form and of name in uninterrupted existence since 1812. The name "New England" was held from 1812 to 1828, when the magazine became the *Boston Medical and Surgical Journal*. In 1928, the name again became *New England Journal of Medicine*.

We are beholden to Dr. Viets for this interesting information about this stalwart publication. Always an appreciative admirer of the contents of the *New England Journal of Medicine*, the *NEW YORK STATE JOURNAL OF MEDICINE* now finds itself viewing with reverence this additional, and until now to us unknown attribute of great age of our northerly sister. We are content to have the respectable, even genteel, name of New England carried forward from generation to generation by such a worthy vessel. The episode of the Boston wild oats, from 1828 to 1928, has already been forgiven, and will soon be forgotten. In another century, not one of us now living will remember it.

In the light of this new learning from the pen of Dr. Henry Viets, historian, we shall henceforth turn the pages of our copies of the *New England Journal of Medicine* gently, with great delicacy. And as they rustle under our disturbing touch, they will remind us of the glories of her youth, the crinolines of Dolores Madison, the exploits of Commodore Perry and Captain Lawrence, and of the *Constitution* and the *Guerriere*, *Old Ironsides*, Tecumseh's Conspiracy, and Harrison at Tippecanoe.

This stalwart, "northerly sister," admitting that great age in itself is not to be taken too seriously and is often, indeed, a subject to be avoided in conversation with the truly old, appreciates

\*McClure, W. B. Chemotherapy in pneumonia cases treated by private practitioners. *Canad. M. A. J.* 45:26-28, 1941.

the admiration, reverence and delicate humor of the *New York State Journal of Medicine*. Perhaps, along with Captain Lawrence, Commodore Perry and Dolly Madison's crinolines, the rustling pages will evoke a memory of the dry, salubrious chuckle of Dr. Holmes.

## OBITUARY

### FREDERICK TAYLOR LORD

1875-1941

FREDERICK TAYLOR LORD was born in Bangor, Maine, on January 16, 1875. His boyhood was spent in Lexington, Massachusetts, and he prepared for college in the public schools of that town. In 1897, he obtained from Harvard his degree of bachelor of arts. His excellent reading knowledge of French and German was doubtless acquired during his college days. Only three years later,—in 1900,—he graduated from the Harvard Medical School. His first knowledge of clinical medicine must have been acquired in the Massachusetts General Hospital during his internship, for at that time there were no clinical clerkships at Harvard and fourth-year students were not allowed in the wards. From the time he entered the hospital as a house officer until he retired as a visiting physician in 1935, his life was intimately connected with the Massachusetts General Hospital.

On finishing his internship, Dr. Lord at once made a beginning in private practice, but at the same time he began research in bacteriology at the Massachusetts General Hospital under the personal direction of Dr. J. Homer Wright, who was as skilled in bacteriologic technic as he was in pathology. At the outset, he received help and inspiration from Dr. William H. Smith, who had worked some time in the laboratory when Dr. Lord was a novice. Undoubtedly Dr. Wright and Dr. Reginald H. Fitz were the two men who influenced him most. His first study published from the laboratory—his second publication—dealt with the influenza bacillus, which he cultivated from 11 cases of acute and 18 cases of chronic infection of the upper respiratory tract. This paper appeared in 1902. Additional studies of the influenza bacillus appeared in 1905. His work on influenza made such a favorable impression on Dr. Osler that he was asked not later than 1905 to prepare the section on influenza for Osler's system of medicine. In this monograph and the two subsequent ones, Dr. Lord presented a detailed analysis of the cases of influenza admitted to the Massachusetts

General Hospital over a period of years. Prior to his work in bacteriology, he published an analysis of 26 cases of so-called "typhoid spine" that he collected from the literature. In its preparation, his knowledge of French and German stood him in good stead.

Diseases of the respiratory tract were always his special interest, dating from his early work with the influenza bacillus. With Dr. Walter James, he contributed the chapter "Diseases of the Pleura" to Osler's system, which was published in 1907.

This early bacteriologic work was carried out in confined quarters. Dr. Means called it a "cubby-hole." Finally, after many years, he acquired a more adequate laboratory, in which he and Dr. Robert N. Nye carried out valuable studies on the biology of the pneumococcus. Pneumonia and tuberculosis were his major subjects of study in later years. He was one of the first to investigate the antipneumococcus serums, and he did much to make serum therapy in pneumonia available to the physicians in Massachusetts through his connection with the Massachusetts Department of Public Health. In collaboration with Drs. Roderick Heffron and Elliott S. Robinson, he wrote two books on the treatment of pneumonia; the second of these dealt with chemotherapy as well as serum therapy.

In 1915, his valuable book, *Diseases of the Bronchi, Lungs and Pleura*, appeared, and ten years later a second edition, thoroughly revised and including a section on pulmonary tuberculosis. In addition to a most thorough study of the literature, this work contains a great deal of original material based on Dr. Lord's experience at the Massachusetts General Hospital and in his private practice. The most careful analysis of medical records is presented. He followed the course of patients for years after he had last seen them. For example, he wrote that of the 65 patients with bronchial asthma in his series whose subsequent courses were known, 11 were completely free from asthma for two to six years after their last visit. This statement, which occupies only three sentences of his text, represents a great deal of laborious work in record making and correspondence with former patients, a task that few physicians would undertake. The book was dedicated to the memory of Dr. Reginald H. Fitz. It is clear that his medical career was largely patterned after that of Dr. Fitz. In the writings of both are the same thorough knowledge of the literature and the same analysis of carefully recorded clinical and pathological observations. This book of outstanding value has never received the recognition it deserved. It is still one of the best treatises on diseases of the respiratory organs.



Dr. Lord was a remarkably successful teacher. Year after year, he gave a course for practitioners, consisting of one exercise a week over a period of many weeks. As many as a hundred physicians attended this course at one time.

His consulting practice for many years was one of the largest, if not the largest, in Boston. The bag filled with diagnostic equipment, which he took with him on consultations, was said to be the largest on record. He examined his patients with meticulous care and made careful records. He made good use of this abundant material. In support of this statement, the following facts are cited. In the birthday volume presented to Sir William Osler in 1919, Lord reported an analysis of 100 cases of pulmonary abscess. In 1925, only six years later, he was able to add 127 cases that he had observed and studied.

During the last seven years, his interests broadened, and problems of public health became his chief concern. He served on advisory committees of both the Boston City and the Massachusetts State departments of health.

As a man, he was kindly, serene and modest. He was charitable of the faults of others and was not given to criticism. But he could speak out fearlessly when an incompetent man was proposed for a position of responsibility. He was in the best sense of the term a self-made man. He carried on his studies and hospital work without pay and largely supported his laboratory at his own expense. He showed the manner of man he was by his work. He talked little and did much. He was a true scholar and scientist, a physician without guile and a man whose memory we cherish and honor.

J. H. P.

## MEDICAL EPONYM

### PAGET'S DISEASE (PRECANCEROUS ECZEMA)

This condition was described by Sir James Paget (1814-1899) in a paper, "On Disease of the Mammary Areola Preceding Cancer of the Mammary Gland," that appeared in the *St. Bartholomew's Hospital Reports* (10:87-89, London, 1874). A portion of the text follows:

I believe it has not as yet been published that certain chronic affections of the skin of the nipple and areola are very often succeeded by the formation of scirrhus cancer in the mammary gland. I have seen about fifteen cases in which this has happened. . . . In all of them the disease began as an eruption on the nipple and areola. In the majority it had the appearance of a florid, intensely red, raw surface, very finely granular, as if nearly the whole thickness of the epidermis were removed; like the surface of very acute diffuse eczema, or like that of an acute balanitis . . . in every case which I have been able to watch, cancer of the mammary gland has followed within at the most two years, and usually within one year. . . .

The formation of cancer has not in any case taken place first in the diseased part of the skin. It has always been in the substance of the mammary gland, beneath or not far from the diseased skin, and always with a clear interval of apparently healthy tissue.

R. W. B.

## MASSACHUSETTS MEDICAL SOCIETY

### COMMITTEE ON MATERNAL WELFARE

#### CASE HISTORY: RUPTURE IN TUBAL PREGNANCY CAUSING FATAL PERITONITIS

A thirty-four-year-old primipara whose past history was entirely irrelevant and whose physical examination was quite normal was seen six weeks after her last catamenia. While working about the house, she was seized with severe abdominal pain, and the physician who responded to her call took her immediately to the hospital, where a diagnosis of ectopic pregnancy was made and operation advised. The patient's husband refused permission for operation, and three days later the patient went home. Eight days after discharge, she returned to the hospital in very poor condition, with a rapid pulse and a low blood pressure. An operation was immediately performed. The abdomen was full of blood, and the contents of the left tube were removed. There were many adhesions about this tube, whose removal resulted in considerable trauma to the adherent intestine. The patient was transfused, and the abdomen was closed, a drain being left at the base of the left adnexa. For twelve days, recovery was satisfactory. At the end of this time, signs of intestinal obstruction appeared, requiring a subsequent operation. At operation, the intestines were found to be kinked and adherent, and an abscess mass was present in the region of the removed left tube. The patient was again transfused, but her condition continued to grow worse until death, which occurred ten days following the second operation.

*Comment.* This fatal case of a rupture in an extrauterine pregnancy was due solely to ignorance or stubbornness on the part of the patient's husband; the medical profession was in no way to blame. The diagnosis was made at the onset of the illness; operation was advised and was refused. The patient went home and returned to the hospital in very poor shape after a second hemorrhage. Had the operation been performed at the time of the first attack, simple surgery would have been sufficient. The operation for the subsequent attack with greater hemorrhage was complicated by the intestinal adhesions surrounding the ruptured tube. These were freed during the salpingectomy, and much raw surface was present that would not have resulted had the operation

been performed earlier, as the surgeon desired. At the second operation, performed because of signs of intestinal obstruction, an abscess was found at the base of the left tube, this was caused by the rupture of the intestine. The patient apparently recovered from the intestinal obstruction and died of general peritonitis.

Each year, several patients die of the complications of tubal pregnancies. Some of these deaths can be attributed to wrong diagnosis on the part of the physician, or to his inability to appreciate the necessity for laparotomy. Some cases are definitely due to ignorance on the part of the patient, who does not seek medical advice when the early signs of irregular bleeding present themselves.

## COMMITTEE ON ARRANGEMENTS

### PROGRAM SUBSTITUTIONS

On account of the illness of Dr Edwin H. Place, Dr Conrad Wesselhoeft has courteously consented to speak. His subject will be "Mumps as a Military Disease."

The Section of Obstetrics and Gynecology will meet in Perkins Hall, Women's Educational and Industrial Union, 244 Boylston Street, instead of at the Tavern Club as previously announced.

WILLIAM T. O'HANLON, *Chairman*

## WAR ACTIVITIES

### CIVILIAN DEFENSE

#### CHEMICAL WARFARE COURSE

Twenty-five physicians from the First, Second and Third defense regions attended a special course, "Medical Aspects of Chemical Warfare Agents," at the University of Cincinnati College of Medicine, February 23 to 26, inclusive under the auspices of the Medical Division of the United States Office of Civilian Defense with the cooperation of the Chemical Warfare Service of the United States Army. It is expected that the class will be repeated for physicians of other regions in the coming months.

It is intended that physicians who have taken this course will be able to set up similar units of instruction in their own localities and will teach both medical and civilian groups. The students were selected by the regional medical officers in the three eastern regions. There was no charge by the university for tuition and materials, the course being offered as a contribution to the war effort. Travel and living expenses of the students were financed locally through state and local defense councils.

## NEW HAMPSHIRE MEDICAL SOCIETY

### NOTE

The new head of the New Hampshire State Board of Health is Dr. Ralph E. Miller of Hanover, assistant dean and associate professor of pathology at Dartmouth Medical School. He succeeds Dr. George C. Wilkins of Manchester, who recently retired after having served in that capacity for many years.

### DEATH

WEBBER — NORMAN B. WEBBER, M.D. of Manchester, died February 22.

Born in Thetford, Vermont, on August 15, 1875, Dr. Webber graduated from the University of Vermont College of Medicine in 1903 and had practiced medicine in Manchester since 1904. He was associated with the Notre Dame and Elliot hospitals. He was a member of the New Hampshire Medical Society and the American Medical Association.

## MISCELLANY

### SCHERING AWARD WINNERS

Winners of the Schering Award for 1941 have just been announced by the Association of Internes and Medical Students. Fred Feldman, 42 Albany Medical College, and Cesare Lombroso, 47 Johns Hopkins University School of Medicine, have been awarded first and second prizes respectively, by the Committee of Judges, a group of outstanding American investigators. Elizabeth Brown, Albany Medical College, and Clarence Denton, Long Island College of Medicine, have been awarded third prize. The subject for the 1941 competition was "The History of Endocrine Research."

The Schering Award, established by the Schering Corporation and conducted by the Association of Internes and Medical Students, offers two tuition scholarships of a year and a half year, respectively, to be granted for the best papers dealing with some aspect of endocrinology submitted by undergraduate medical school students in the United

### DEATHS

BREFFN — JOHN J. BREFFN, M.D. of Lowell, died February 3. He was in his fortieth year.

Born in Lowell, the son of the late John J. and Harriett (Greenhalge) Breen, he received his degree from St. Louis University School of Medicine in 1928. After serving his internship at St. John's Hospital, Lowell, Dr. Breen began general practice in Lowell. He was associated with the staffs of St. John's Hospital, the Lowell Visiting Nurses Association and the Lowell Day Nursery, and was a member of the Massachusetts Medical Society and the American Medical Association. At the time of his death, he was awaiting call for active service with the United States Army.

WHEELER — JOHN B. WHEELER, M.D. of Burlington, Vermont, died May 1. He was in his eighty-ninth year.

Born in Stowe, Vermont, Dr. Wheeler received his degree from Harvard Medical School in 1879. He was an intern at the Massachusetts General Hospital. From 1881 to 1924 he was associated with the surgical department of the University of Vermont College of Medicine — as instructor, clinical professor and professor. He was one of the founders of the American College of Surgeons and the New England Surgical Society. He was a fellow of the Vermont State Medical Society and the American Medical Association, and was a former member of the Massachusetts Medical Society.

Two daughters and a sister survive him.

States or Canada. In all, papers were submitted by students representing twenty-four medical schools, an indication of the wide interest and response occasioned by the competition.

Plans for the Schering Award competition for 1942, which will again be sponsored by the Association of Internes and Medical Students, are being formulated. The subject for this year's paper, as well as the full panel of judges, will be announced shortly.

## ANNUAL PRIZE SUBSCRIPTION

The annual prize subscription offered by the *New England Journal of Medicine* for the best undergraduate contribution to the *Tufts Medical Journal* has been awarded to Mathew Ross, '42, for his paper "Acute Appendicitis of Childhood and Its Differential Diagnosis," which appeared in the March, 1942, issue. The paper "Constitutional Medicine," by D. A. Freedman, '43, received honorable mention; it appeared in the November, 1941, issue of the journal.

## NOTES

At the recent meeting of the American Heart Association in New York City, Dr. Paul D. White, of Boston, was elected president for the ensuing year.

Two important appointments to the staff of the Harvard Medical School, effective July 1, were recently announced by the University. Dr. Rene Jules Dubos has been appointed George Fabyan Professor of Comparative Pathology and Professor of Tropical Medicine, to succeed Dr. Ernest E. Tyzzer, who becomes professor emeritus. Dr. George W. Thorn has been appointed Hersey Professor of the Theory and Practice of Physic and Physician-in-Chief of the Peter Bent Brigham Hospital, to succeed the late Dr. Soma Weiss.

## REPORT OF MEETING

### NEW ENGLAND PEDIATRIC SOCIETY

A regular meeting of the New England Pediatric Society, held at Longwood Towers on January 14, was presided over by Dr. R. Cannon Eley. An obituary of the late Dr. Kenneth Blackfan was read. The speaker of the evening was Dr. Joseph W. Ferrebee, of the new Harvard School of Dental Medicine, who discussed the dental problem as related to the practice of pediatrics.

At present, the cost of dental care is equal to or even greater than that for medical treatment. Twenty per cent of those examined by the military authorities in the present selective-service group are found to have reason for rejection in the condition of their teeth. The repair of teeth, which accounts for two thirds of the dentists' work, is much more costly than prophylactic treatment. Furthermore, this need will become more urgent with the natural regression of the teeth attendant on our civilized habits of eating and preparing foods. It is well known that milling removes 90 per cent of certain vitamins, for example.

The problem for the pediatrician springs partly from the fact that the calcification of the primary dentition takes place from midterm on, whereas secondary calcification occurs from term through early childhood. Contrary to popular belief, primary dentition is not unimportant, for at that time normal chewing habits begin that result in proper spacing of the teeth and development of

the jaw. And proper spacing of the teeth prevents the dirt and pyorrhea that accompany faulty cleaning. Furthermore, caries may be spontaneously walled off in a few weeks by secondary dentine if the person is placed on good general home care and proper diet.

At present, the maximum incidence of visits to the dentist occurs in the age group from fifteen to twenty-one years, whereas the minimum is in those from three to eleven years. For better results, these should be reversed, so that proper prophylaxis might be carried out. The essential factors in prevention of later dental troubles are proper home care of the teeth, an adequate diet and frequent visits to the dentist at an early age.

## BOOK REVIEWS

*Lectures on War Neuroses.* By T. A. Ross, M.D. 12°, cloth, 116 pp. Baltimore: Williams and Wilkins Company, 1941. \$2.00.

This brief volume is a valuable addition to the subject of war neuroses. It was written by a physician who had a large experience in World War I and subsequently continued to be interested in civilian neuroses in his practice of medicine. He has been in touch with the subject in World War II, and he gives some brief notes on the experiences of the English soldier escaping from Dunkirk and the effect of bombing on the public.

The volume is divided into only four chapters: one presents a preliminary discussion of neuroses in general; the second deals with the acute war neuroses; and the third and fourth discuss the more chronic conditions. The material in these chapters has been given as lectures at medical centers in the last twelve months.

Full of sound common sense and written by a man who is completely familiar with his material, this little book is an outstanding contribution to the subject. It is, moreover, timely, and should be put in the hands of every medical officer in charge of soldiers, sailors or civilians likely to suffer from neuroses incident to modern warfare.

*Outline of Industrial Medical Practice.* By Howard E. Collier, M.D. (Edin.), Ch.B. 8°, cloth, 440 pp. Baltimore: Williams and Wilkins Company, 1941. \$5.00.

Out of the kaleidoscopic development of manufacturing processes during the past two decades, industrial medicine has emerged as a new field in which the general practitioner finds few landmarks or familiar paths. It is especially to orient the run-of-the-mine physician in the problems of modern industrial medicine and to furnish the plant physician with a working guide to administrative practice that this book has been prepared.

In addition to providing an exceptionally concise and practical handbook on all phases of occupational hygiene this work is unique in emphasizing the importance of group illness in industrial medicine. Since occupational disease is something more than the aggregate of the illnesses of the individuals in the group, the plant physician as well as the health officer, must learn to think in terms of possible common causes of group illness. The sector on industrial psychology is the clearest and most constructive discussion that the reviewer has seen of that vexed but significant field.

The bibliography is well chosen for the physician who may wish to look farther into some of the sources of industrial medicine.

(Notices on page xi)

# The New England Journal of Medicine

Copyright, 1942, by the Massachusetts Medical Society

VOLUME 226

MAY 28, 1942

NUMBER 22

## MEDICINE AND AIR SUPREMACY\*

JOHN F. FULTON, M.D.†

NEW HAVEN, CONNECTICUT

GEORGE CHEYNE SHATTUCK, the younger (1813-93), whose father, George Cheyne Shattuck, the elder (1784-1854), left the bequest that led to the founding of this lectureship, died early in 1893, and Osler,<sup>1</sup> who gave the fourth lecture of the series in that year, chose for his subject "Tuberculous Pleurisy," a theme in which the younger Shattuck had been interested since his early days in Paris, when he studied under the great French clinician, Louis. Shattuck's son, Frederick Cheever Shattuck (1847-1929), was, like his father and grandfather, a great force in New England medicine. The Shattucks were men of humor, forthright candor and passionate loyalty to the traditions of this country. Their humor is well illustrated in a lively encounter between Frederick Cheever Shattuck and Harvey Cushing, who gave the Shattuck Lecture in 1913.<sup>2</sup> Dr. Shattuck had read Cushing's account of the Western Reserve and its traditions,<sup>3</sup> and was horrified to find the word tomahawk misspelled. Dr. Cushing, his secretariat and the Cleveland proofreaders had all passed "tommyhawk"—spelled like "tommy-gun." This was too much for Frederick Cheever, who immediately commandeered conveyance to the Peter Bent Brigham Hospital, and, wearing a pair of enormous plus fours, dashed in the side door of Dr. Cushing's office to tell him that the Moseley Professor of Surgery, who had been born in the Western Reserve out among the Indians, should know the spelling of tomahawk; not content with this, he wrote Cushing a letter referring him to the *Century Dictionary*.

\* \* \*

I have said that the Shattucks were men of intense loyalty to this country's traditions, and when your committee requested aviation medicine as the subject of this discourse, it seemed obviously

a theme wholly appropriate for a lecture devoted to the memory of this remarkable line of American physicians; moreover, a topic with military implications is not without precedent, for just twenty-five years ago, — in June, 1917, — Dr. Walter B. Cannon gave a Shattuck Lecture on traumatic shock.<sup>4</sup> In accepting the honor, I have, however, taken on a heavy responsibility, and one that for various reasons is embarrassing.<sup>5</sup>

The National Research Council and the Office of Scientific Research and Development have followed the policy of classifying as "confidential" or "secret" all topics having to do with offensive instrumentalities of war. The airplane is clearly such an instrumentality, as are many of the devices within the plane designed to improve the performance of the pilot in his rapid, high-altitude maneuvers; so that medicine, perhaps for the first time in its history, has come to be divided, so far as war is concerned, into offensive and defensive spheres. Advances that have to do with increasing the effectiveness of human performance in combat become military secrets, and cannot now be openly discussed. Defensive measures, on the other hand, designed for treating the wounded, either civilian or military, or for prophylaxis, as by inoculation, fall into the category of defensive measures and can be freely described. Aviation medicine falls squarely across the broad categories of offense and defense, and I am therefore obliged to devote attention primarily to the defensive phases of the subject.

It has become obvious, even to the most casual observer, that air supremacy will determine the outcome of the present war. Shipping still has vast importance and we look carefully to our tonnage, but all the ships of the United Nations would become virtually useless without command of the air. Supremacy in aviation is not wholly a question of more and faster planes with greater firing power than the enemy. This, to be ant, but equally so is the

\*The Shattuck Lecture, delivered at the annual meeting of the Massachusetts Medical Society, Boston, May 26, 1942.  
†From the Laboratory of Physiology, Yale University School of Medicine.  
‡Assistant Professor of Physiology, Yale University School of Medicine.

well-selected, well-trained and adequately protected flying personnel. The performance of modern aircraft has far outstripped the physiological limitations of the pilot. The newer combat planes can fly higher than is compatible with life, even when the fliers are breathing pure oxygen. They can perform maneuvers causing centrifugal force of such intensity that blood tends to be drawn away from the brain, a condition that results in transient blindness (blacking-out) and unconsciousness. And, finally, the range of the modern four-motored bombers—some of which can remain for twenty-four hours in the air—has raised problems of pilot fatigue, severe stresses and strains from cold, psychological tension and loss of sleep that impair the performance of flying personnel. It is the responsibility of medicine in its broadest sense, including psychology, psychiatry, physiology and the special branches of clinical medicine, to protect flying personnel from these and many other hazards that they face. The role of the physician in both the offensive and defensive phases of the war effort has therefore become increasingly vital for broad military strategy.

Air supremacy involves not only flying personnel but ground personnel. It is estimated that for every man in the air there are nine or ten men on the ground, both in civilian airlines and in military aviation; men on the ground are as essential as the men in the air, and if the Army should wish 100,000 pilots it must recruit 1,000,000 men. Air supremacy also extends to the men in the aircraft factories, who are exposed to special hazards peculiar to aircraft production. I cannot speak of industrial hazards in aircraft plants, but they are real and their successful handling rests with industrial physicians. In an aviation plant recently visited, 600 from a total of 30,000 employees were treated daily for accidents or illness occurring in the plant—that is, 2 per cent of the total personnel became ill or were injured each day. This is far higher than one would wish or anticipate, and yet with the vast expansion of the past twelve months, such injuries are to some extent inevitable. In a plant that is not expanding, injury rates diminish, but usually only as rapidly as the measures taken for their prevention. The need for industrial physicians in all phases of the war effort continues to be enormous.

To give a more general idea of the scope of aviation medicine, I shall describe a classified bibliography of the subject that is now in the process of publication.

#### LITERATURE OF AVIATION MEDICINE

In recent months, my associates, Dr. and Mrs. Ebbe C. Hoff, and I have had the responsibility

of searching out, listing and classifying all available literature bearing on the medical aspects of aviation. The project was proposed near eighteen months ago, and the labor is now completed, for the bibliography will be published within a few weeks.<sup>6</sup> The subject matter covers a vast range, the principal topics being indicated by the main chapter headings of the bibliography:

1. History and General Aspects of Aviation Medicine.
2. The Special Physiology of Aviation. (This section is divided into nineteen subsections including all the organ systems and special senses.)
3. The Special Pharmacology of Aviation.
4. The Special Psychology of Aviation.
5. Aeromicrobiology. (Bacteriology and immunology in aviation and high altitudes.)
6. Diseases and Accidents in Aviation and Conditions Simulating Flight.
7. Selection and Assessment of Efficiency of Flight Personnel.
8. Training, Performance and Fatigue of Flight Personnel.
9. Protection of Flight Personnel: Preventive medicine and therapeutics of aviation.
10. Aviation and Public Health.
11. Organization of Aviation Medicine.
12. Special Problems.
13. General Studies in Aviation Medicine.
14. Bibliographies.

It may be of interest that, although approximately six thousand separate items were for the author index contains some nineteen thousand names, from which one must infer that those who write on the subject generally write in trios. And this expresses what some of us gradually come to realize: that research endeavor in this field is inevitably co-operative. The flight surgeon uses a pilot or some fellow flight surgeon as a subject of an experiment, sometimes in air, sometimes in a decompression chamber, sometimes in a human centrifuge. When decompression experiments are involved, five or six people generally constitute a team, and their names may appear as co-authors of the report.

The bibliography itself cuts across the scientific periodical literature of all phases of the world, countries, articles from about 1920 onwards having been cited. Of course, the bibliography includes only articles in medical journals.

In passing, one may mention that from the standpoint it would be impossible to work out purely for medical journals. On this point we were fortunately forewarned and at the start adopted the conventions of *A World List of Scientific Periodicals* as a basis for abbreviations; this made possible the citation in conveniently abbreviated form of any scientific journal in any language, without serious confusion.

In surveying this literature, we were impressed by the large number of Japanese articles on aviation medicine. Much more striking, however, was

fact that about thirty Russian journals were represented in the bibliography, embodying a vast and well-co-ordinated literature on the subject—far ahead, incidentally, of that of Japan.

There is a widespread feeling that bibliography is a dull preoccupation reserved for spinsters and old maids of the male sex. Actually, it is far from that, for careful analysis of the literature of any subject reveals trends of research, and in the bibliography under consideration, it has exposed trends and emphasis of far-reaching international significance. The Germans, for example, began publishing papers on the effects of high acceleration in aircraft five years before the flight surgeons of the United Nations had given any general consideration to the problem, and everyone must realize what the dive bomber has meant to the Axis war effort. For better or for worse, the Allies have depended largely on horizontal bombing, but with our fast fighters we are quickly learning the significance of high acceleration, and are studying the modes of counteracting its effects on aircraft personnel.

#### PROBLEM OF ANOXIA

The responsibility of carrying on research in the more academic phases of aviation medicine falls largely to the civilian laboratories, although one looks forward to research institutes within the military services that will continue with active investigative endeavor in times of peace. But in the present war crisis, it is clearly up to the civilian scientists to undertake the long-range problems, and in aviation medicine the most basic of these is a study of the adjustments of the body to anoxia. There are many aspects of the problem as yet imperfectly understood,—individual variations, variations of the individual,—factors that aid the body in making the adaptations, all of which involve fundamental physiological, biochemical and endocrinological research; the aim in view is to increase knowledge of the processes involved and to search out ways of improving human performance in the higher altitude ranges. To use the language of aviation, the basic problem is to raise the aviator's "ceiling." But from the purely academic standpoint, we wish first to extend our knowledge of the processes involved.

In his excellent monographic review on the effects of anoxia in the body, Van Liere<sup>8</sup> gives a broad picture of the manifold changes that occur when the body is exposed to low oxygen partial pressure. In adjusting, for example, to a fall of half an atmosphere, giving an equivalent altitude of 18,000 feet, there is a veritable ionic cataclysm between blood and tissues and renal tubules, accompanied by a shift of the blood pH to the alkali-

line side, with an extensive loss of sodium and chloride ions in the urine. Van Liere, however, makes little attempt to elucidate the important problem of how these ionic shifts are integrated. What organ responds in the first instance to the lowered oxygen partial pressure? From the work of Cannon<sup>9</sup> and of Gellhorn and his collaborators,<sup>10, 11</sup> it is known that the sympathetic system is exquisitely sensitive to anoxia and that many of the adjustments arise from the direct stimulating action of low oxygen tension on the central neurons of the sympathetic system. From the sympathetic comes the reflex mobilization of idle red blood cells from spleen, bone marrow and other reservoirs, and a vast series of vasomotor readjustments designed to improve the circulation of vital organs is brought about, also reflexly, through interaction of the sympathetic and parasympathetic systems. No one, however, appears previously to have suggested that the ionic shifts essential for anoxic acclimatization are likewise mediated through reflex channels. The evidence to date is incomplete, but suggestive, and it turns largely on recent developments bearing on the part played by the adrenocortical hormone in anoxia.

#### Anoxia and Adrenal Cortex

Two papers published by French flight surgeons at the end of the last war suggested that the asthenia that certain aviators developed after repeated missions to high altitudes was due to adrenal insufficiency. Ferry<sup>12</sup> observed urinary retention of nitrogen and alkali, low blood pressure and pathological heart sounds in a group of over-fatigued aviators, and he was led on the basis of these findings to the conclusion just mentioned. The paper of Josué<sup>13</sup> was based on a study of physiological and psychological alterations in fatigued pilots. But since at that time there was no clear distinction between the adrenal medulla and the cortex, the suggestion can remain only of historical interest. More recently, Armstrong and Heim<sup>14</sup> found on exposing rabbits for four hours a day to an atmosphere equivalent to 18,000 feet that, in the early stages, hypertrophy of the adrenal gland resulted and was followed later by degenerative changes in the adrenal cortex. In his well-known book on aviation medicine, Armstrong<sup>15</sup> later pointed out that overfatigued pilots, especially those subjected to many high-altitude missions, developed symptoms strikingly similar to those seen in early Addison's disease.

Sundstroem,<sup>16, 17</sup> whose early studies on the adaptation of man to high altitudes are well known, was led some years ago to study the relation of the adrenal glands to acclimatization

and, independently of Armstrong and Heim, confirmed the existence of adrenal hypertrophy resulting from anoxia; in his monograph about to appear from the University of California Press, he<sup>18</sup> shows that the degree of adrenal hypertrophy can be roughly correlated with the extent to which the oxygen partial pressure is diminished. All animals exposed to diminished atmospheric pressure during the period of acclimatization tend to lose weight. This loss of weight is shared, according to Sundstroem, by all organs of the body except the adrenal cortex (and possibly the kidney); the adrenal hypertrophy is therefore regarded as something specific to the anoxic state. On the basis of the hypertrophy, Sundstroem asked himself whether this might not indicate increased secretion of the glands. He set out to obtain a direct answer to the question in two ways. In the first place, adrenal steroids were extracted from tissues, such as the heart and liver, from control animals at sea level and from groups exposed to the high-altitude ranges; the tissues of the latter animals invariably showed a larger proportion of adrenal steroid than the corresponding tissues in animals at sea level.

More impressive, however, was the study of Giragossintz and Sundstroem,<sup>19</sup> in which it was found that adrenalectomized animals could not survive in the high-altitude ranges and that it took twenty times more crude extract of the adrenal cortex to maintain rats at 20,000 feet than it did at sea level. This clearly suggested that to maintain the body at high altitude increased secretion of adrenocortical extract is essential.

The problem has recently been taken up anew in my laboratory by Langley and Clarke,<sup>20, 21</sup> who have confirmed the fact that adrenal hypertrophy develops in rats exposed to 20,000 feet; and in adrenalectomized animals, they find that at sea level the maintenance dosage for an average adult rat is 0.5 cc. of total extract a day (Wilson), or 0.03 mg. of desoxycorticosterone acetate. At 20,000 feet, a rat on this maintenance dose rapidly loses weight and dies, and Langley and Clarke find that 2 or 3 cc. of total extract is essential at that altitude and that 1 mg. of desoxycorticosterone is required. When acclimatization has taken place, however, after one week at 20,000 feet, the maintenance dose can be reduced to the sea-level amount.

Langley found, as had Gerald Evans,<sup>22, 23</sup> that exposure of a fasting rat to an altitude of 20,000 feet for twenty-four hours causes an elevation of both the blood-sugar and liver-glycogen levels. This suggests that Compound E, the carbohydrate fraction of the adrenocortical secretion, is mobilized in conditions of anoxia. But the desoxycorticosterone fraction appears also to be mobilized, since Langley has found in dogs exposed to an altitude of 20,000 feet

that a marked increase occurs in sodium and chloride and also in potassium excretion. Following adrenalectomy, dogs subjected to anoxia failed to show the sodium and chloride excretion, although potassium loss continued. The failure of the sodium, chloride and carbohydrate adjustments in adrenalectomized animals exposed to anoxia indicates that the presence of adrenal extract is apparently essential to make the bodily adjustments to altitude, and one naturally wishes to know how the adrenal cortex is specifically activated—whether directly by the blood stream, or in some way through the nervous system. Langley,<sup>20</sup> in discussing the question, remarks: "It is possible that the increase in sodium, chloride and urine volume observed in the normal animal exposed to anoxia was brought about by increased excretion of these specific fractions [desoxycorticosterone] of the adrenal cortex. This observation suggests that the adrenal cortex is capable of secreting certain components of the whole extract independently of the others."

The recent important work of Dr. George Thorn,<sup>24</sup> the newly appointed Hersey Professor of Medicine at the Harvard Medical School, has also established in animals that a large increase in sodium, chloride and potassium excretion occurs on exposure to anoxia, and he has found conspicuous nitrogen retention in man under these conditions. Treatment of adrenalectomized animals with the so-called "carbohydrate-regulating" factor caused a striking increase in sodium, chloride and water excretion, but no increase in potassium. Thorn and his collaborators<sup>25-27</sup> have just given an account of the effect on rats, rabbits and dogs of intermittent exposure to altitudes equivalent to 18,000 and 27,000 feet. They have confirmed Armstrong and Heim's<sup>14</sup> observation that adrenal hypertrophy develops in consequence of such repeated exposure in rabbits (and also rats); they have found, moreover, that the adrenalectomized animal fails to survive repeated "flights" to these altitudes, and that their capacity for adjustment can be restored by administration of adrenocortical hormone.

From the studies of Collip<sup>28</sup> and his students, it appears probable that the adrenal cortex is normally activated, not by the blood stream directly, but rather by the adrenotropic hormone of the anterior pituitary. The ingenious work of Uotila<sup>29, 30</sup> indicated that the thyrotropic hormone is under the direct control of nerve centers in the hypothalamus whose axons passed down the pituitary stalk, and that the reaction to cold results from thermal stimulation (via the blood) of the hypothalamic centers. Since the adrenal cortex also plays a large part in the reaction to cold and to anoxia, it is likely that the primary activation of the adrenal cortex comes from the hypothalamus through the adrenotropic hormone. Favoring this is the fact, originally disclosed by Gerald Evans<sup>22</sup> and recently confirmed by Catchpole,<sup>31</sup> that the chronically hypophysectomized rat has

no greater altitude tolerance than the adrenal-ectomized animal

All this brings one to a far clearer concept of the mode of integration of the bodily adjustments to altitude. The part played by the respiratory center in the medulla has long been recognized. Mobilization of red cells and the reflex adjustments of the heart and circulation arise in part from direct stimulation of the chemoreceptors of the carotid body, as well as from the direct effect of low-oxygen tension on the sympathetic system; there appears to be further reflex control, through the centers in the hypothalamus, of the ionic pattern and carbohydrate level of the blood. Undoubtedly, when the complete picture has been put together, the posterior pituitary gland will also be found to play a part in these adjustments through the influence of its antidiuretic hormone on the kidney tubules. This strongly suggests that the bodily adjustments to anoxia are in large measure integrated by the central nervous system.

#### SAFETY IN CRASHES

The military phases of aviation medicine are rigidly practical. General academic research is encouraged at some of the larger bases and institutions, but for the immediate purposes of the war effort a group of practical problems has arisen for which solution is required in a matter of months. Combat fliers, for example, are constantly exposed to rough landings under black-out conditions, or to crash landings when machines are disabled, and the question arises whether mechanical factors for safety, similar to those introduced within the past few years in automotive design, cannot be adapted to aircraft. This raises the question of the factors responsible for injuries, fatal and otherwise, in air crashes. Close study of the large literature on air crashes indicates that impact of the body, especially the head, with some solid part of the aircraft is generally the cause of death or of serious injury, even in minor accidents. When the body or the head strikes something that yields, as when the flier is thrown through a fabric roof or the windshield, the victim generally escapes serious injury. What, then, are the basic factors that govern the degree of injury in such circumstances?

The most significant clues have come from two sources. De Haven's<sup>12</sup> analysis of nonfatal suicidal leaps from high buildings, and a study, for which Denny Brown is largely responsible, of the effects of sudden acceleration on the head.

**Nonfatal suicidal leaps.** In a series of recent papers, De Haven<sup>12-13</sup> has drawn attention to some remarkable cases of suicidal leaps from high buildings that proved not to be fatal. A number

of such cases—in which all data were available concerning the exact distance of the fall, the position of the body during the fall and on landing, and the character of the surface that the body struck—permitted him to draw certain generalizations on the nonfatal leap, the victim generally landed flat on the back or flat on the stomach, so that the long bones or the head was not driven into the trunk. But more interesting is the fact that a slight degree of cushioning of the head, as in landing in a garden plot instead of on a cement sidewalk, prevented concussion and serious injury of other parts. A typical case may be cited<sup>13</sup>.

A twenty-one year-old woman, mentally depressed because of an amorous disappointment, took a room on the tenth floor of a hotel, consumed half a bottle of whiskey, and leapt in her nightdress to the street below—a free fall of 93 feet. She landed squarely on her back in a small garden in which the earth had been freshly turned, her head, back and legs sinking into the earth to a depth of 4 to 6 inches. A hand, which struck the cement border of the garden plot, suffered a fracture to a small bone in the wrist, but except for this and a fractured rib she was uninjured, suffered no concussion, and could walk without assistance. Her height was 5 feet, 7 inches, and her weight 115 pounds.

The important point about this and similar cases is that the head experienced a brief interval of deceleration, instead of an abrupt impact on a rigidly solid object. De Haven calculates that the girl's body was falling at a rate of 73 feet a second (50 miles an hour) at the time of the impact, and that the deceleration distance, which amounted to 4 to 6 inches of garden turf, must have taken place in a small fraction of a second; the rate of deceleration was 166 *g* (1 *g* = 32 feet per second per second). There is a vast difference between being decelerated from 50 miles an hour in 0.001 second and being decelerated in 0.1 or even in 0.01 second. Little attempt has been made so far to measure these brief but vital deceleratory time intervals in relation to injury.

A more complex case occurred several months ago in New York and is mentioned because of the relatively long distance of the fall. A woman leaped from the seventeenth floor, falling 144 feet, and landed in a "steamer-chair" position on a metal ventilator box 24 inches wide, 18 inches high and 10 feet long. The force of her fall, De Haven points out, crushed the structure to a depth of 12 to 18 inches. Both arms and one leg extended beyond the area of the ventilator, with resultant fractures of both bones of both forearms, the left humerus and the left os calcis. The woman remembered falling and landing, but had no marks



Java, India, Africa, the Mediterranean and the North Atlantic sea lanes be given a sense of the importance of the contribution they have rendered, be given a sense of the part that they may still be able to contribute if put back into active service. I am not speaking as a psychiatrist, or even as a practical surgeon, but essentially as a layman. I have, however, had opportunity to survey the literature and have seen hospitals filled with sick men, seriously injured men, of the fighting forces of Britain; I cannot too vigorously emphasize the value of maintaining the morale of the injured man, of allowing him to take part in the care of others more seriously incapacitated than himself, and of giving him opportunity to discuss combat problems with those who have been placed before their injury in military situations similar to his own.

\* \* \*

Expansion of the air corps of both the United States Navy and Army has created an unprecedented need for medical personnel. The Navy within the year expects to complete training of more than 1000 air medical officers including several hundred flight surgeons, and Colonel David Grant, Air Surgeon of the Army, authorizes me to say that the Army Air Forces have now in service some 2300 medical officers and that an expansion is expected within the year to bring a total of 19,000 flight surgeons and aviation medical officers. If this demand is filled, it would alone absorb all the graduates of Class A medical schools in the United States during the past three years.

This war is probably more challenging to the physician than any other conflict in the world's history. Those who serve, especially those who serve the air forces, must have special knowledge; they must be cognizant of this, cognizant also of the part that they can play in maintaining air supremacy, and of re-establishing the right of free men to live in peace.

#### REFERENCES

1. Osler, W. Tuberculous pleurisy. *Boston M. & S. J.* 129:53-57, 81-85, 109-114, 134-138, 1893.
2. Cushing, H. Concerning diabetes insipidus and the polyurias of hypophyseal origin. *Boston M. & S. J.* 168:901-910, 1913.
3. *Idem.* *The Western Reserve and Its Medical Traditions.* 33 pp. Cleveland: Privately printed, 1924.
4. Cannon, W. B. The physiological factors concerned in surgical shock. *Boston M. & S. J.* 176:859-867, 1917.
5. Fulton, J. F. Physiology and high altitude flying: with particular reference to air embolism and the effects of acceleration. *Science* 45:207-212, 1942.
6. Hoff, E. C., and Fulton, J. F. *A Bibliography of Aviation Medicine.* Prepared for the Committee on Aviation Medicine, National Research Council. Springfield, Illinois: Charles C Thomas (in press).
7. Smith, W. A. *A World List of Scientific Periodicals Published in the Years 1900-1933.* Second edition. 779 pp. London: Oxford University Press, 1934.
8. Van Liere, E. J. *Anoxia: Its effect on the body.* 269 pp. Chicago: University of Chicago Press, 1942.
9. Cannon, W. B. *The Wisdom of the Body.* Second edition. 333 pp. New York: W. W. Norton & Co., 1939.
10. Gellhorn, E. Fundamental principles in the adjustment reactions of the organism to anoxia. *Ann. Int. Med.* 14:1518-1532, 1941.
11. Gellhorn, E., and Lambert, E. H. The vasomotor system in anoxia and asphyxia. *Illinois M. & Dent. Monogr.* 2(3):1-71, 1939.
12. Ferry, G. Les signes prémonitoires de l'asthénie des aviateurs. *Compt. rend. Soc. de biol.* 82:637, 1919.
13. Josué, O. L'asthénie des aviateurs. *Compt. rend. Soc. de biol.* 82:641-643, 1919.
14. Armstrong, H. G., and Heim, J. W. The effect of repeated daily exposures to anoxemia. *J. Aviation Med.* 9:92-96, 1938.
15. Armstrong, H. G. *Principles and Practice of Aviation Medicine.* 496 pp. Baltimore: Williams & Wilkins Co., 1939.
16. Sundstroem, E. S. Studies on adaptation of man to high altitudes. *Univ. California Publ., Physiol.* 5:121-132, 1919.
17. *Idem.* The physiological effects of tropical climate. *Physiol. Rev.* 7:320-362, 1927.
18. *Idem.* *Adrenal Cortex in Adaptation to Altitude, Climate and Cancer.* Berkeley: University of California Press (in press).
19. Giragosintz, G., and Sundstroem, E. S. Cortico-adrenal insufficiency in rats under reduced pressure. *Proc. Soc. Exper. Biol. & Med.* 36:432-434, 1937.
20. Langley, L. L. *The Role of the Adrenal Cortex in the Reaction to Low Atmospheric Pressure.* A dissertation presented to the Faculty of the Graduate School, Yale University, in candidacy for the degree of Doctor of Philosophy, 1942.
21. Langley, L. L., and Clarke, R. W. The role of the adrenal cortex in the reactions to low atmospheric pressure. *Yale J. Biol. & Med.* 14:529-546, 1942.
22. Evans, G. The effect of low atmospheric pressure on the glycogen content of the rat. *Am. J. Physiol.* 110:273-277, 1934.
23. *Idem.* The adrenal cortex and endogenous carbohydrate formation. *Am. J. Physiol.* 114:297-308, 1936.
24. Lewis, R. A., Thorn, G. W., Koepf, G. F., and Dorrance, S. S. The role of the adrenal cortex in acute anoxia. *J. Clin. Investigation* 21:33-46, 1942.
25. Thorn, G. W., Jones, B. J., Lewis, R. A., Koepf, G. F., and Mitchell, E. R. The role of the adrenal cortex in anoxia. The effect of repeated daily exposures to reduced oxygen pressure. I. Experiment on rats. *Am. J. Physiol.* (in press).
26. Jones, B. F., Thorn, G. W., Lewis, R. A., and Kennedy, T. J., Jr. The role of the adrenal cortex in anoxia. The effect of repeated daily exposures to reduced oxygen pressure. II. Experiments on rabbits. *Am. J. Physiol.* (in press).
27. Thorn, G. W., Jones, B. F., Lewis, R. A., and Eisenberg, H. The role of the adrenal cortex in anoxia. The effect of repeated daily exposures to reduced oxygen pressure. III. Experiments on dogs. *Am. J. Physiol.* (in press).
28. Collip, J. B., Anderson, E. M., and Thomson, D. L. Adrenotropic hormone of anterior pituitary lobe. *Lancet* 2:347, 1933.
29. Uotila, U. U. The regulation of thyrotropic function by thyroxine after pituitary stalk section. *Endocrinology* 26:129-135, 1940.
30. *Idem.* Hypothalamic control of anterior pituitary. *A. Research Nerv. & Ment. Dis., Proc.* (1939) 20:580-588, 1940.
31. Catchpole, H. R. Personal communication.
32. De Haven, H. Miraculous safety. *Air Facts* 4:21-26, 1941.
33. *Idem.* Mechanical analysis of survival in falls from heights of fifty to one hundred and fifty feet. *War Medicine* (in press).
34. Committee on Aircraft Accidents. *Aircraft Accidents Method of Analysis.* United States National Advisory Committee for Aeronautics Report No. 576. 10 pp. Washington: Government Printing Office 1941.
35. Denny-Brown, D., and Russell, W. R. Experimental cerebral concussion. *Brain* 64:93-164, 1941.
36. Cairns, H. Head injuries in motor-cyclists: the importance of the crash helmet. *Brit. M. J.* 2:465-471, 1941.
37. Bradford, F. K., and Spurling, R. G. *The Intervertebral Disc with Special Reference to Rupture of the Annulus Fibrosus with Herniation of the Nucleus Pulposus.* 158 pp. Springfield, Illinois: Charles Thomas, 1941.
38. Grow, M. C., and Armstrong, H. G. *Fit to Fly: A medical handbook for fliers.* 387 pp. New York: D. Appleton-Century Co., 1941.
39. Love, J. G., and Walsh, M. N. Intraspinous protrusion of intervertebral disks. *Arch. Surg.* 40:454-484, 1940.
40. Symonds, C. P. Sciatic pain. *Lancet* 1:186, 1942.
41. Spurling, R. G. Personal communication.
42. Watson-Jones, R. Rehabilitation in the Royal Air Force. *Brit. M. J.* 1:403-407, 1942.

VITAMIN B<sub>1</sub> AND ENDURANCE\*

PETER V. KARPOVICH, M.D.,† AND NATHAN MILLMAN, M.Sc.‡

SPRINGFIELD, MASSACHUSETTS

RECENT reports<sup>1</sup> have indicated that the administration of vitamin B<sub>1</sub> may increase muscular endurance in subjects on a diet deficient in that vitamin. This effect is explained on the basis of the role of vitamin B<sub>1</sub> as an oxidative catalyst employed in the chemical process involved in muscular contraction. For this reason, men engaged in hard muscular work use more vitamin B<sub>1</sub> than those in sedentary occupations, and the amount suggested by investigators for workingmen and athletes is more than 300 international units daily. Yet Stiebeling and Phippard<sup>2</sup> report that a large number of people in the United States live on a diet poor in this vitamin.

The possibility of increasing human stamina and endurance, coupled with a fear of a probable lack of the vitamin, has been impressed on the public mind, and the use of synthetic vitamin B<sub>1</sub> has become widespread. It is employed not only in cases in which a definite vitamin deficiency has been found but also, in a more general way, as insurance against a possible lack of it. Tablets including thiamin chloride are supplied free in some industries, college athletes are given it, and even professional baseball players must take it to remain in the good graces of the management.

Recognizing the importance of vitamin B<sub>1</sub> and its strikingly beneficial effect in patients whose diet has been deficient in thiamin content, we questioned whether an excess of vitamin B<sub>1</sub> could increase the capacity of the human organism for work. At various colleges where either "shotgun prescriptions" including vitamin B<sub>1</sub> or this vitamin alone was being given to varsity athletes, no striking and convincing (at least for outsiders) results were obtained. At Springfield College, Coach Charles Silva had been giving vitamin B complex, but no appreciable effect on the performance in swimming could be detected. The weakness in most of these "experiments" lies in the fact that they lacked controls. Usually, every member of the team received the same dose, and quantitative measures of performance were often impossible. How, for example, can one evaluate the effect of a certain vitamin on basketball players, football players and so forth? It is only when the amount of energy used can be measured, as

in track running or swimming, that the tests become objective.

McCormick,<sup>3</sup> who attempted to improve endurance by giving his subjects a daily dose of 5 mg of thiamin chloride in tablet form, used two tests: breath holding and arm holding. After one week of administration of vitamin B<sub>1</sub>, he noticed definite improvement as measured by these tests. Since, in our judgment, McCormick's appraisal of the vitamin intake of his subjects was not convincing, and the results of the tests were not indicative of the vitamin effect, we decided to repeat his experiments.

**Arm-holding test.** Sixty-nine subjects, all of college age, were tested for the time they were able to hold their arms horizontally. For convenience, these men were divided into three groups (Table 1) in the first group, who were simply

TABLE 1 Summary of Preliminary Arm Holding Tests

ARM HOLDING TIME min	NO PEP TALK	PEP TALK	EMPHATIC PEP TALK
	NO OF SUBJECTS	NO OF SUBJECTS	NO OF SUBJECTS
9 or less	8	5	1
10 to 29	7	14	15
30 to 119	2	2	6
120 to 190	2	2	6
260	—	—	1
Totals	17	23	29

told to hold their arms outstretched as long as possible, the holding time ranged from 6 to 108 minutes, in the second group, who were given a "pep talk" with a reference to McCormick's record (which was erroneously announced as 135 minutes and was actually 145 minutes), the range of endurance varied from 8 to 135 minutes, in the third group, who were tested two days after the first two groups and, naturally, had been talking about the "remarkable" feat of holding the arms outstretched for 135 minutes, an especially emphatic "pep talk" was given and the range varied from 9 to 260 minutes.

Forty-one of the 50 men whose arm holding times were less than 30 minutes were given either 5 mg of thiamin hydrochloride a day or a placebo (5 mg of lactose).<sup>§</sup>

A week later, the second test was given, the range varying from 5 to 77 minutes in the group who did not receive the vitamin, and from 7 to

\*From the Physiology Department, Springfield College.  
†The author of physiology, Springfield College (on leave of absence) at present, Research Section, School of Aviation Medicine, Randolph Field, Texas.  
‡Member, Research Laboratory, Ortho Products Incorporated, Linden, New Jersey.

§The vitamin and placebo tablets were generously furnished by McKesson and Robbins Incorporated, Bridgeport, Connecticut.

79 minutes in the men who did (Table 2). In the latter, 8 out of 16 improved, and in the former, 12 out of 25.

Of particular interest is the fact that some of the subjects who were given the preliminary test were on a high vitamin B<sub>1</sub> diet, and some were on a low diet. To the first group belonged the varsity swimmers, and to the second some of the wrestlers who were trying to lose weight. Of the 4 swimmers, 1 could not hold his arms out-

The arm-holding test has been used by other investigators<sup>4, 5</sup> to detect the changes in endurance due to various modifications of the diet. In view of the evidence here presented, the reliability of this test as an indication of muscular endurance should be seriously questioned. Persons who are easily affected by suggestion, or even by auto-suggestion, are apt to give a better performance in this test.

*The breath-holding test.* This is one of the routine class tests given at Springfield College in a course of instruction in the physiology of exercise. During hundreds of tests, it has been observed that the psychologic factors greatly influence the time of breath holding. Nevertheless, we used a group of 20 men for this experiment. They were given two breath-holding tests in succession, and then half the subjects were put on a diet containing 5 mg. of thiamin chloride a day for a week, and half on one containing 5 mg. of lactose a day. No effect of vitamin B<sub>1</sub> on breath-holding ability was observed.

CONCLUSIONS

Vitamin B<sub>1</sub> deficiency in apparently normal college students cannot be discovered by means of either the arm-holding or the breath-holding test.

These tests may be greatly affected by psychologic factors, and are therefore not reliable indications of the degree of muscular endurance.

REFERENCES

1 Williams, R. D., Mason, L. H., and Smith, B. F. Induced vitamin B<sub>1</sub> deficiency in human subjects. *Proc. Staff Meet., Mayo Clin.* 14:787, 1939.  
2 Stuebeling, H. K., and Phipard, E. F. *Diets of Families of Employees, Wage Earners and Clerical Workers in Cities*. United States Department of Agriculture Circular 507. 141 pp. Washington: Government Printing Office, 1939.  
3 McCormick, W. J. Vitamin B<sub>1</sub> and physical endurance. *M. Rec.* 152:439, 1940.  
4 Benedict, F. G., Miles, W. R., Roth, P., and Smith, H. M. *Human Vitality and Efficiency under Prolonged Restricted Diet*. Carnegie Publication 280. 701 pp. Washington: Carnegie Institution of Washington, 1919.  
5 Fisher, I. The influence of flesh eating on endurance. *Yale M. J.* 13:205-221, 1907.

TABLE 2. Summary of Arm-Holding Tests with and without Vitamin Therapy.

IMPROVEMENT OVER FIRST TEST %	VITAMIN GROUP	CONTROL GROUP
0-10	4	1
11-20	0	1
21-30	0	2
31-40	0	1
41-50	2	1
51-60	0	1
61-70	0	2
71-80	1	1
81-90	0	1
91-100	1	0
101-200	3	2
201-300	2	6
301-400	0	2
401-500	2	1
501 or more	1	1
Decrease in ability	0	2
Totals	16	25

stretched for more than 10 minutes, and 2 of the others, for more than 60 minutes. Of the 2 wrestlers, one held the position for 161 minutes, and the other for 260 minutes (4 hours and 20 minutes).

These tests showed either that all the men had a sufficient amount of vitamin B<sub>1</sub>, which was questionable in the wrestlers, or that arm holding cannot be used as a test for the effect of the vitamin in apparently normal people, or for vitamin B<sub>1</sub> at all, because the test is definitely affected by psychologic factors, such as a "pep talk" and the competitive elements involved.

## KELOIDS AND THEIR TREATMENT\*

LOUIS H. NASON, M.D.†

BOSTON

**K**ELOIDS may be defined as an exaggerated growth of scar tissue. In this exaggeration, they appear to defy to some extent the normal rules of growth, and have accordingly been considered a bridge or link between normal reparative processes and actual neoplastic changes. However, unlike neoplastic growths, the keloid process is initiated from normal fibroblastic cells solely by trauma. These cells produce the keloid by carrying on their normal function—although to an exaggerated degree. This exaggeration continues even after excision, and in fact, the tendency to recur is the most characteristic feature of the growths. Were this not so, keloids would cease to be a problem.

In their growth, keloids become thicker and heavier and actually extend out into adjacent normal skin, well beyond the border of the original injury. This quality of extending beyond the site of the original injury is a pathognomonic feature of keloids and helps differentiate them from hypertrophic heaped-up scars or cicatrices, which develop at the site of suppurative or the site of previous loss of tissue, are limited entirely to the areas involved by suppuration or trauma, and gradually shrink and become less conspicuous. Keloids always project above the level of the surrounding skin, but extend very little, if at all, into the underlying subcutaneous tissue. In fact, in secondary abdominal operations involving the excision of a keloid occurring in a previous incision, relatively little scar tissue may be encountered in the subcutaneous fat, although the skin keloid may be very heavy.

## ETIOLOGIC FACTORS

Trauma is always the precipitating etiologic factor in the production of keloids. Keloids probably never occur without the preliminary destruction of cells by some form of physical or chemical violence. However, only certain persons consistently develop keloids after moderate trauma. This tendency indicates some sort of fibroblastic diathesis, varying in intensity among races and individuals. Furthermore, the sensitivity of the fibroblasts to substances provoking proliferation and growth may change as the patient gets older and as the rate of growth and metabolism alters. This accounts for the relative scar-

city of keloids beyond the age of fifty. Indeed, it is very rare in the aged, whereas it is rather frequent in the young. In a survey of 50 cases of appendectomy for chronic appendicitis in children between the ages of five and fifteen years, various degrees of keloids were noted in 28 cases—a high percentage.

There are also local influencing factors. Keloids occur only rarely on the face, forehead, hands and feet, front of the neck, axilla, inguinal region, anal region and perineum, whereas they are common around the ears, sides and back of the neck, abdomen and chest (particularly in women). Keloids seldom, if ever, occur in incisions placed in natural flexion creases, although they may occur in incisions or scars running across flexion creases. The only explanation for this phenomenon seems to be the manner in which tension is applied to different areas in the body. It will be noted that in those regions in which keloids seldom occur, the skin and underlying tissues are subject to constantly changing degrees of tension and stress. These areas are very often moved and shifted in the course of ordinary activity. There is a considerable amount of constantly changing stress and strain in the flexion creases and in the perianal and perineal regions. On the contrary, where keloids occur frequently, the skin is under the normal degree of tension but remains almost constantly so with relatively little motion and change. In areas where there is no skin tension whatever,—as in the scrotum and in the upper eyelids,—keloids do not occur. One other interesting phenomenon is the rarity of keloids in the hairy regions of the body. All these local factors are of primary importance in the selection of sites for incisions and in the prevention and treatment of keloids.

## TREATMENT

The treatments advocated for keloids have been legion. If one is shocked at the lack of rationale of some of them, one may at least admire their ingenuity. Lesieur<sup>1</sup> injected oil of creosote, and Smyth<sup>2</sup> used formalin. Attempts at digestion of the keloid were made by Ahlsvede,<sup>3</sup> who used a mixture of pepsin and hydrochloric acid. Hoffman,<sup>4</sup> in his paper advocating radiation as the treatment of choice, lists twelve methods of treatment collected from the literature, but many more can be gathered without difficulty. These vary

\*From the Plastic Clinic, Beth Israel Hospital.  
†Instructor in surgery, Harvard Medical School; assistant in surgery, Beth Israel Hospital.

from Sheehan's<sup>5</sup> "capillary" drainage to iodine ionization, advocated by Grain.<sup>6</sup> Cannon<sup>7</sup> painted the lesions with trichloroacetic acid to thin out the keratotic layers and then subjected the lesions to roentgen radiation. This author also recommends desiccation, preceded and followed by x-ray treatment. Unna<sup>8</sup> reported a patient cured of a keloid by the application of pressure renewed weekly for three months.

No one treatment produces good results in all keloids, but considerable success may be attained consistently if all factors in each case are carefully

orthodox ones. The suture material should be as fine as possible—preferably a No. 000000 dermal plastic suture. A cutting-edge needle is far less traumatizing than a round needle. If the wound is not under tension, the sutures should be removed in forty-eight to seventy-two hours. Very accurate approximation, of course, needs no further emphasis.

Constant excessive tension must be released either as a preliminary to further surgery or radiation or in the process of excision. If a keloid is excised and the edges approximated under

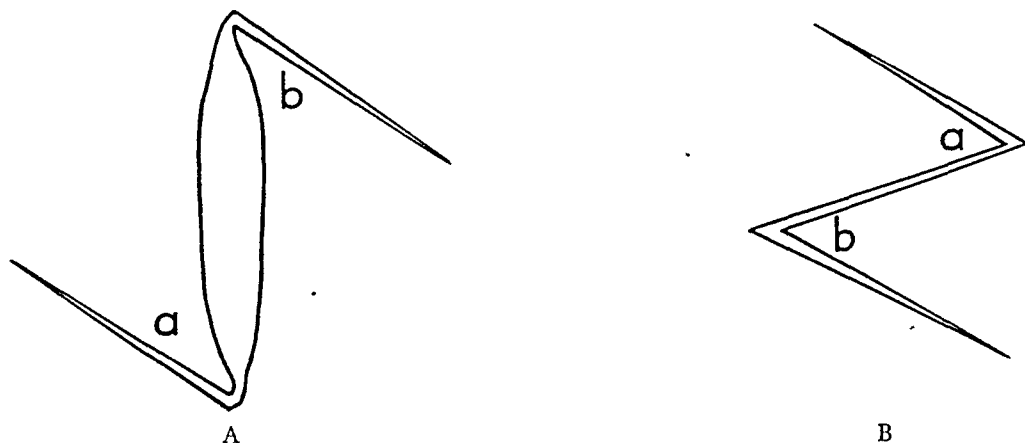


FIGURE 1. *The Z Plastic.*

*A—the keloid has been excised, and two parallel incisions made, defining two flaps (a and b); B—the flaps are transposed and sutured; note that the lines of tension are rotated through 90°.*

considered. A keloid in a given patient is not a stereotyped condition. The very realization that one is dealing with a lesion that occurs because of a specific type of diathesis and may be influenced by local factors will in itself serve to orient one in the consideration of the proper treatment. Certain essential principles must be adhered to. These are the avoidance of further trauma, the release of constant excessive tension, the application of pressure, and the careful use of surgery in addition to radiation.

Rough handling, vigorous massage, careless surgery and the application of traction serve to aggravate or reproduce the keloid. Whatever procedure is carried out, it is well to remember that trauma produced the lesion to begin with, and that by no stretch of the imagination can one believe that trauma can also effect a cure. Nowhere in the realm of surgery does a satisfactory end result depend so much on scrupulous, atraumatic technique as in the surgical removal of keloids. The use of a sharp knife, fine-pointed forceps and sharp, cutting-edge, atraumatic needles is necessary. The exact type of suture material or stitch does not matter. Subcuticular sutures are apt to give poorer approximation and more reaction than the more

exactly the same conditions of tension as previously existed, the keloid will certainly recur. It is for this reason that simple excision is inadequate. The essential fact is that the direction of established stresses should be changed if possible. A Z plastic is of invaluable aid in such a situation (Fig. 1). This produces a rotation of the vertical portion of the Z to the horizontal, and rotates the direction of the maximum tissue tension 90°. Simple excision may be carried out successfully on the abdomen, the upper extremity and the neck.

Subsequent tension may be avoided by judicious choice of flap plastics in place of free skin grafts. Free grafts of all sorts tend to contract and pull the surrounding tissues around them. When a pedicle graft may be used in place of simple suture of skin graft, it is preferable. Releasing incisions are very useful provided they do not jeopardize the cosmetic result. If they can be placed in a natural crease or within a hairline, they serve as a valuable adjunct. Satisfactory results may be obtained in the excision of a keloid from the back of the neck by the use of a parallel releasing incision placed 3 or 4 cm. higher up in the scalp itself. The combination of the releasing incision and the flap is illustrated by a type of plastic very

suitable for keloids over the broad surfaces of the body, such as the chest and back (Fig. 2). This consists of excision of the keloid and then the making of a V-shaped incision a suitable distance from the defect so that a flap may be raised and transplanted to obliterate the original defect. The V-shaped defect in the new incision is then closed in a Y-shaped approximation.

The use of radiation for the treatment or prevention of recurrences of keloids is by no means so logical or consistently successful as some reports indicate. The old, well-developed keloids are

utilized with comfort. The simplest method is to fashion a throat stick, a piece of dental impression compound or a piece of heavy felt to conform to the shape of the keloid. This mold is then strapped tightly to the keloid. Strappings should be changed weekly. If adequate pressure is applied, a remarkable change is noted after the first week, but if the pressure is not continued, the keloid quickly resumes its original prominence. The strapping, therefore, should be renewed weekly, with no interruption for at least six to eight weeks, and pos-

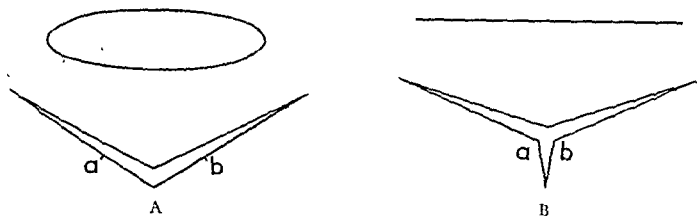


FIGURE 2. *The V-Y Plastic.*

*A—the keloid has been excised, and a V-shaped incision made, parallel to the long axis; B—the original defect is closed in a straight line, and the V-shaped defect as a Y; such closure produces no tension.*

extremely resistant; the younger ones respond well to radiation. Hence, if radiation is to be employed, well-developed keloids should first be excised, so that they may be supplanted by a young keloid. The best results reported are in those series in which radiation, from three to five days postoperatively, is given after surgical excision. It is assumed that at that time the young proliferating fibroblasts are most sensitive to radiation. In fact, radiation delayed a few days after excision yields better results than radiation given into the open wound at the time of or within twenty-four hours of operation.

Excision of the keloid, in addition to any plastic procedure necessary to relieve tension, followed by radiation in moderate dosage from three to five days postoperatively is what I believe to be the method of choice in most cases.

The use of pressure, when applicable, may yield excellent results with no risk of recurrence. It is not rare to note keloid formation in the lower half of a low abdominal scar, whereas in the upper portion—where the imprint of the elastic of an undergarment or belt may be seen—no keloid is present. The ischemia produced by the pressure arrests overproduction of scar tissue. Slight but constant pressure may be applied to some portions of the body over long periods. Over the extremities, the abdomen and the shoulders, pressure by means of adhesive strapping may be

sibly longer. This method is particularly applicable to young keloids, which are more vascular and contain less collagenous material than the old ones. The local anemia induced by the pressure has more effect on the more vascular lesions. Obviously, pressure is not applicable to the face, the neck, the front of the chest and parts of the back. Pressure may be utilized in the prevention of recurrences by the simple expedient of keeping the incision covered with a strip of adhesive plaster for many weeks. The light, even pressure of the adhesive results in a much smoother, softer scar, with practically no elevation above the skin.

If keloids recur, the average time of recurrence is two or three weeks. Evidence of return may even be noted within two weeks. However, if keloids do not recur within six to eight weeks, one may consider subsequent recurrence extremely remote.

## RESULTS

The following results were obtained from observations on fifty-one keloids in 49 patients. The cases were grouped according to the method of treatment, as follows: excision and reapproximation; radiation; excision and radiation; and pressure. Table 1 indicates the results obtained. For the purposes of tabulation, a result was considered satisfactory when the keloid was not longer present, or when it was strikingly improved. A fair

result was indicated by definite, but partial, improvement, and an unsatisfactory result by a case in which the keloid remained unchanged, recurred or became more marked.

SUMMARY AND CONCLUSIONS

The exact etiologic factors in the production of keloids are not known, but there is sufficient

TABLE 1. Results of Four Methods of Treatment.

TREATMENT	NO. OF CASES	RESULT		
		SATIS-FACTORY	FAIR	UNSATIS-FACTORY
Simple excision and reapproximation.	12	2	2	8
Radiation .	9	4	1	4
Excision and radiation (3 to 5 days).	19	10	6	3
Pressure .	11	7	2	2
Totals	51	23	11	17

evidence to indicate wide variations in racial and individual susceptibility. In addition, certain local factors, particularly the manner in which local skin tension is applied, may be shown to have a determining influence in the occurrence of keloids. Areas in which skin tension is constant are apter to be the site of keloids, whereas in areas where

there are frequent changes in tension of the skin, — such as the creases, — keloids rarely occur. In these areas, keloids do occur if the original scar is sufficiently extensive or if it extends across the normal lines of tension.

Treatment consists in the avoidance of further trauma, the release of constant and excessive tension, the careful use of surgery, in addition to radiation, and, rarely, the use of pressure alone. Pressure may also be employed to prevent recurrence after excision. When pressure cannot be utilized, the treatment of choice consists in excision of the keloid, in addition to any plastic procedure necessary to relieve tension, followed by radiation in moderate dosage beginning from three to five days postoperatively.

474 Beacon Street

REFERENCES

1. Lesieur, M. Traitement des chéloïdes par les injections d'huile créosotée. *Bull. Acad. de méd., Paris* 79:40-42, 1918.  
2. Smyth, J. Treatment of keloid. *Brit. M. J.* 2:811, 1913.  
3. Ahlswede, E. Digestion of keloids, cicatrices and buboes with pepsin-hydrochloric acid. *Arch. Dermat. & Syph.* 3:142, 1921.  
4. Hoffman, W. J. Treatment of keloids. *Arch. Phys. Therapy* 15:135-138, 1937.  
5. Sheehan, J. E. A clinic in reparative surgery. Examples of treatment for keloids, unilateral facial paralysis and of the various applications of skin graft. *S. Clin. North America* 12:341-356, 1932.  
6. Grain, R. Traitement des chéloïdes cervicales par l'ionisation iodée. *Bull. et mém. Soc. de méd. de Paris* 142:345, 1938.  
7. Cannon, A. B. The treatment of x-ray burns and other superficial disfigurements. *New York State J. Med.* 40:391-399, 1940.  
8. Unna, H. L. Cited by Hoffman.<sup>4</sup>

MEDICAL PROGRESS

OTOLOGY: THE TREATMENT OF DEAFNESS IN THE LIGHT OF RECENT ANIMAL EXPERIMENTATION\*

M. H. LURIE, M.D.†

BOSTON

TO treat the deaf successfully has been the ambition of all otolaryngologists. Unfortunately, the otologist is immediately on the defensive when the patient announces that he is deaf. The mental sigh of relief when large plugs of cerumen are found is almost audible, for here is something to be done that will give relief. As for the other types of deafness, except for certain conditions such as the acute suppurative and the secretory ear, the otologist, after establishing the diagnosis, considers the case hopeless and subconsciously prays that the patient will not return.

Reprints of articles in this series are not available for distribution, but the articles will be published in book form. The current volume is *Medical Progress Annual, 1940* (Springfield, Illinois: Charles C Thomas Company, 1941. \$4.00).  
\*Read by invitation at a meeting of the Pacific Coast Oto-Ophthalmological Society, Los Angeles, California, May 26, 1941.  
From the Departments of Otolaryngology, Harvard Medical School, and the Mosher Laboratory, Massachusetts Eye and Ear Infirmary.  
†Assistant professor of otology, Harvard Medical School; surgeon in otolaryngology, Massachusetts Eye and Ear Infirmary; consulting otolaryngologist, Massachusetts General Hospital.

This defeatist point of view is not due to lack of knowledge of methods of treatment used at present, but to a failure to realize that many types of deafness can be helped even though the condition cannot be cured. To approach this subject intelligently, one must have an understanding of the present conception of how people hear.

Hearing is not a function of the middle or inner ear alone but is in reality a phenomenon of the brain resulting from the interpretation of nerve impulses coming to it from the sense organ for hearing, the organ of Corti. The basic requirements for hearing are a normal sense organ to receive the sound waves and a normal brain to interpret the messages received from the sense organ. The middle ear and its structures are aids and refinements for acute hearing, but are not essential to hearing, for which other apparatus can be substituted in certain types of deafness.

The statement that a normal brain is essential for hearing may raise doubts in many minds, but I should like to point out that all animals of the mammalian group (man is one) hear in the same manner but that the interpretation of the sense-organ stimulation varies tremendously with the development of the brain. The newborn infant does not hear until he has learned to interpret the stimuli received, and as the interpretative power of the child increases so does his hearing, for it is from this ability to interpret and repeat the sounds heard that speech and its accessories, reading and writing, have developed.

The membranous labyrinth, with its vestibular and cochlear sense organs, is well known and requires no detailed description. I should like to draw attention to the way these two sense organs work. They both depend on movements of fluid to stimulate them. The vestibular apparatus requires movement of the endolymph—that is, movement of the fluid inside the membranous vestibular structures. The cochlear mechanism depends on movement of the perilymph, which is outside the membranous cochlea. Thus, the vestibular portion can be called the endolymphatic system of the membranous labyrinth. The cochlear portion can be called the perilymphatic system of the membranous labyrinth. This distinction is important and is more fully discussed below.

The organ of Corti is the sense organ for hearing. It consists of specialized neuroepithelial hair cells, which are probably stimulated by movement of the basilar membrane. The membranous cochlea is so arranged that the stimulation is through the perilymph, as one can easily see when examining the relation of the membranous cochlea (scala media) to the perilymphatic spaces, the scala vestibuli and tympani. The organ of Corti is not concerned in the question of how this movement of the perilymph is obtained, but once it is produced in sufficient strength to cause movement, it responds and the resulting sensation is hearing.

Thus, deafness divides itself into two types. The first is that in which the organ of Corti itself is involved: the hair cells may degenerate, and as a result, there is an inability of the organ of Corti to respond to the fluid-pressure changes, even though these pressures are made in a normal manner. This lack of response has been called "nerve deafness," because it was thought to be a degeneration of the cochlear nerve; "variable deafness," because there are a great many types of hearing loss with this condition; and "perception deafness," because the deafness is a result of failure of the sense organ to respond to the stimuli sent to it. These three terms indicate the same type of deafness. In the second type, the fluid-

pressure changes are prevented, or made more difficult to produce, in the perilymph. The organ of Corti is normal, but with lack of stimulation, there is no response. This type of deafness, which is due to the inability of the external air-pressure changes or air sound waves to be transmitted to the perilymph, is therefore called "transmission deafness" or "middle-ear deafness," for these structures are involved.

The middle ear and its structures have to do with the changing of air-wave pressures into fluid-wave pressures. Anything interfering with this function results in a loss of hearing. The plugging of the external ear by wax or debris is the simplest type to remedy. Pathologic conditions of the middle-ear structures, such as fusion of the malleus and incus or adhesions around the ossicles, which prevent them from moving freely, the thickened and retracted drum, perforations of the drum, chronic suppuration and acute suppuration of the middle ear, all cause deafness for air-borne sounds, for they interfere with their transmission. Otosclerosis acts in a similar manner, that is, by an interference with air-borne sounds. Sound waves transmitted by the vibration of the bone structures surrounding the membranous cochlea are not interfered with, and the normal organ of Corti responds readily to them.

Thus, it is the duty of the otologist to use all the knowledge he has to overcome this transmission difficulty. Mechanical means, such as the hearing trumpet and the fan that is held by the teeth, to conduct sound waves to the cochlea have been employed. The new hearing aids are of great benefit to many. Most of these patients can be helped if the otologist will take time and effort to find the method to be used. A great many patients with large posterior perforations are helped by the application of a paper drum, which can be made out of patipar paper, is waterproof and stays in place very readily. One can be pleasantly surprised at the amount of hearing improvement obtained by the use of a paper drum. The making of absorbent-cotton drums should be known to all, and many patients have used them for years.

One of the finest appliances for patients with a posterior perforation or absence of the drum or ossicles, and even in those who have had radical mastoid operations, is the Pohlman<sup>1</sup> apparatus. This device has proved very satisfactory, even in cases that are discharging and in dry cavities. The principle on which it is based is the replacing of the former normal human transmitting apparatus with one similar to the bird's middle ear. This appliance, when in place, can be worn for long periods. Patients have had them in as



long as eight or nine months and have heard remarkably well with them.

All the methods described above depend for their good results on the ability of the apparatus used to change the air-borne sounds into fluid waves, and a normal or almost normal organ of Corti to respond to the stimulation. It would be unwise to expect these aids to enable a patient with a diseased or degenerated organ of Corti to hear better, for no matter how good the transmission, there is no sense organ to respond.

Thus, the fenestration operations of Holmgren, Sourdille and Lempert are sound from this point of view, and they should work so long as the perilymph can be stimulated by air-pressure changes, that is, by sound waves. It must be perilymph stimulation and not endolymph stimulation. Stimulation from endolymph-pressure changes results in vestibular responses such as dizziness and nystagmus. The fact that a case of fistulization responds to pressure changes of the endolymph is not necessarily an indication that the perilymph is also responding to air-pressure changes. The difficulty with the fenestration operation is not that it will not work, but in keeping the fistula in such a state that the perilymph will continue to respond to sound waves. New-bone formation, fibrous bands and even a complete blocking of the perilymphatic spaces around the fistula will nullify all the efforts of the operation. The fistula operation is a definite step forward in the attempt to cure transmission deafness. Whether such deafness is due to otosclerosis or middle-ear deafness is immaterial. The main question to be kept in mind with this operation is, Has the patient a normal or nearly normal organ of Corti to respond to the resulting stimulation? If not, the operation should not be done.

The present technical difficulties will be overcome in the near future. Only time will tell if the regeneration of bone or the other mishaps that have occurred in this operation can be prevented. Thus, it does not behoove one to take sides regarding this operation, but to allow time and further experimentation to tell the story. Again, one must remember that the new technics are not easily acquired. No otologist at the present time should expect to get results in his early operations. In fact, it should be emphasized that it is an operation for the younger generation of otologists to attempt and then only after an arduous and thorough training in its technics and indications. There is no doubt that the fenestration operation will have a definite place in the otology of the future.

Middle-ear or transmission deafness, except otosclerosis, results from neglect of mild middle-ear disease caused by the common cold, with its blocked eustachian tube. There is a great deal of literature on this subject, but many otologists

still do not realize that it is their duty to warn the public and to emphasize the fact that a great deal of middle-ear deafness can be prevented. The children with the neglected mild catarrhal or secretory ears are the future middle-ear deaf persons of adult life.

Middle-ear deafness is a problem that has been attacked in a great many ways, for its chief fundamental pathology is the prevention of sound waves reaching the organ of Corti, and this can be overcome. The great challenge to the otologist is nerve deafness of the acquired or inherited type. Before undertaking the treatment of this disorder, one must understand it. Is it nerve degeneration or degeneration of the sense organ itself? Nerve deafness can theoretically occur in one of three ways: by destruction of the central nerve pathways for auditory stimuli, such as hemorrhage in the brain, intracranial tumors and arteriosclerosis with degeneration of the auditory cortex; by degeneration of the cochlear nerve secondary to meningitis, as in cerebrospinal meningitis, influenzal meningitis, syphilis, acoustic neuromas in the external auditory meatus and toxic conditions that may attack the nerve endings; and by degeneration of the sense organ itself—that is, degeneration of the internal and external hair cells, accompanied by secondary degeneration of the cochlear nerve.

In nerve deafness, one characteristic stands out. The patient can hear the sounds but cannot make the words out accurately. He is always complaining that people do not articulate properly. They mumble, and as a result he cannot hear. What does he miss? He misses the very fine, high sounds of small intensity. These high-frequency sounds make the difference between words that have similar vowels but different consonants. If the intensity of the spoken words is increased, the patient has less difficulty in distinguishing them. He has trouble hearing people on the telephone and can never hear everyone at the dinner table or in a room filled with people talking at the same time. Noisy places bother him. He hears best when conversing with a single person.

There is no evidence from these people that their brains cannot interpret, but there is an indication that the auditory impulses received by the brain from the organ of Corti are the result of sound waves not received accurately. If the cochlear nerve is at fault, one would expect complete blocking off of the impulses from the organ of Corti, with a resulting complete loss of hearing for the area involved. This does happen in some cases, with complete loss of tones above 5000 but with normal responses below these frequencies. Others may have definite islands of deafness. But the majority of nerve-deaf people hear all tones from 64 to 8000 cycles per second when they are made

loud enough; this shows that the nerve itself is not primarily responsible for this type of deafness.

From experimental studies on animals and human beings, the evidence at present is that the end organ itself is primarily the cause of nerve or perception deafness.<sup>2,3</sup> The following data were obtained from animals, for it is from this material that the treatment of nerve deafness can be evaluated.

It has been known for years that people exposed to loud sounds for long periods become deaf, and the type of deafness that develops is a nerve deafness. It has been called blacksmiths' deafness, boilermakers' deafness, riveters' deafness and, recently, aviators' deafness. Animal experimentation definitely shows that this type of deafness is the result of degeneration of the organ of Corti, the external hair cells go first, and then the internal hair cells. The testing of the electrical response of the organ of Corti of experimental animals showed a typical loss of function similar to that of the nerve deaf person. This was confirmed by the fact that the person subjecting these animals to the sounds also lost his hearing in a similar manner. Exposure of human subjects to extremely loud sounds for short periods gave similar results. Fortunately, the human organ of Corti recovered from these experimental exposures, but there is no question that if the exposures were repeated more frequently and for longer periods, there would be a marked and permanent loss of hearing owing to degeneration of the hair cells.<sup>3</sup>

Chemical poisoning of guinea pigs in which prolonged doses of quinine were given also resulted in degeneration of the hair cells. Animals were found that were deaf secondary to disease of unknown origin. They also had degeneration of the external hair cells, and some degeneration of the internal hair cells. In the first group of animals (deaf as result of disease), there was also degeneration of the cochlear nerve. In the first two groups, the cochlear nerve gave no evidence of gross degeneration.<sup>3</sup>

This experimental work demonstrates that the nerve-deaf person has a degeneration of the external hair cells scattered over a large area of the organ of Corti. As a result, he has lost his ability to interpret the fine and weak sounds of high frequency, and this loss causes his deafness. If the sounds are made louder, his interpretation is better, because internal hairs begin to respond to the stimuli and the hearing is improved.<sup>2</sup>

The nerve deaf person first appears for treatment when he has already lost between 20 and 40 decibels of hearing. The reason is that the deafness comes on gradually and over a long period. It may be years before he notices that he no longer can hear as other people do. To treat this patient

with the expectation of restoring hearing is futile. To treat with the expectation or hope of preventing further loss or even slight improvement is justifiable.

A number of factors causing degeneration of the hair cells may be grouped as follows. Toxic poisons such as alcohol to excess, tobacco, quinine and salicylic acid compounds, chronic infections, with toxic absorption affecting the end-organ apparatus; endocrine disturbances; and certain diseases, such as pneumonia, influenza, mumps, syphilis and meningitis, attacking either the nerve or the organ of Corti. Any one or all in various combinations can cause nerve deafness.

One must remember, in treating these patients, that no cure can be promised or expected. In the majority of cases, nothing can be done except to try to prevent further damage to the organ of Corti. Degenerated hair cells cannot be restored. All one can do is to try to prevent further degeneration, and even this may be impossible. It is true that every now and then one seems to improve the hearing in some of the nerve deaf people. This is usually the result of improving the general health of the patient or of treating the endocrine defect if it can be found. In all cases, one should build up the general physical condition of the patient. Vitamins or estrogenic substances, it must be understood, are not cures for deafness. They cannot restore degenerated or absorbed hair cells and nerve ganglia that are gone.

Tinnitus that is possibly due to nerve irritation may be temporarily relieved by the use of the vitamin B complex in large doses. Selfridge<sup>4</sup> and others have reported their results. The experimental work with vitamins, as reported by Melinby<sup>5</sup> and Covell,<sup>6,7</sup> was done on very young and rapidly growing animals. The experiments performed on adult animals have not, as yet, produced the same results. It is not rational to expect that vitamins will restore to normal function a sense organ that for years has been degenerating because of disease or lack of vitamins. The majority of people with this complaint are over thirty years of age.

A great many of the nerve-deaf patients also have middle ear conditions that can be helped, and it is in the treatment of such conditions that the best results have been obtained, not in the actual restoring of the organ of Corti, but in the improvement of the mechanism that has to do with transmission of sound, so that the patient can use his sense organ to its greatest efficiency.

Thyroid has also been used as a cure for deafness. The only cases I have found that were helped were definite hypothyroid cases in which the loss of hearing was due to the slow cerebration of

the patient rather than to a true loss of sense-organ cells.

There is also a group of patients that inherit deafness, not the congenitally deaf, but persons who begin to lose hearing at definite ages, from puberty to forty-five years; their histories indicate that members of their families have sustained the same loss. Nothing can be done for them. It is interesting that animals also have this tendency to inherit deafness. In these animals, the deafness is primarily due to a degeneration of the hair cells of the organ of Corti.<sup>8</sup> Otosclerosis is considered an inherited disease in which there is first a middle-ear and later a nerve deafness.

In recent experimental work on human beings, it has been demonstrated that tinnitus of definite pitch is due to irritation of the organ of Corti itself. The pitch of the tinnitus could be determined on either side of the traumatic lesion caused. Further proof of the organ of Corti as the cause of tinnitus with definite pitch was found in experiments on human beings in which the cochlea was stimulated electrically.<sup>9</sup> It was impossible to stimulate the cochlear nerve and obtain definite pitch. The sound reported on stimulation of the cochlear nerve was a general buzzing or hissing noise, but no accurate placing of pitch was possible. That the nerve was being stimulated was proved by the fact that there was also response of the vestibular nerve, which was being stimulated at the same time.

In a number of cases, in which the hearing loss was due to labyrinthitis, one could not get responses for tones except where the organ of Corti was present and definite tone islands were found. Patients with middle-ear deafness due to large perforations, ossiculectomy or radical mastoid operations responded to tones up and down the range very accurately, and could match the tone with air-borne sounds sent to the other ear. These experiments on human subjects have definitely shown that stimulation of the nerve itself cannot enable the patient to hear. The sense organ must be present.

In studies being done on traumatic deafness, it has been possible to demonstrate trauma to the organ of Corti. In one of these experiments, it took several days for the subject's hearing to come back to normal. Studies on animals showed similar results and indicate that disorganization of the hair cells and not the nerve is the primary cause of traumatic deafness.<sup>2, 3</sup>

One must view with a great deal of caution all claims for curing deafness that depend on systemic treatment. I know of no drugs or methods of treatment that will restore hair cells once they have degenerated. Again, prevention and not attempt at cure is the only hope.

The organ of Corti is the last of the special senses to be developed. It is a most sensitive sense organ, and is easily affected by a great many factors, such as disease, chemical poisons and trauma. No other sense organ in the body reacts so quickly to physical disturbances. In fact, in some ways, the cochlea is an indication not only of physical well-being but also of actual age in its relation to the body structures. Thus, at the present time, methods of treating the nerve-deaf person are limited to the removal of poisons, either chemical or toxic, and to the improvement of the general health of the patient.

\* \* \*

It should be emphasized that one can and should do more to help the patients with middle-ear deafness. It takes time, and progress may be slow, but with hearing appliances and with the future possibilities of the fenestration operation one should be more willing to undertake the treatment of these cases.

In nerve deafness, the general physical well-being of the patient should be raised to as high a level as possible. Vitamins and other drugs that are necessary to bring about this condition should be used. Foci of infection causing toxic absorption should be removed. Toxic substances, such as tobacco, alcohol and drugs, should be completely eliminated; partial discontinuance is of no benefit. The results will not be cures, but in all probability, healthier persons who will be able to use to the utmost the hearing that is left.

In many ways, man by his inventions has caused a great deal of deafness. Nature makes few noises that are capable of causing deafness. Man has made many, such as airplanes, riveting machines, explosives, tanks and machinery. One must appeal to the acoustical engineer to reduce, so far as possible, the man-made noises that are causing this delicate and very sensitive apparatus of hearing, the organ of Corti, to degenerate.

483 Beacon Street

#### REFERENCES

1. Pohlman, A. G. The present status of the mechanics of sound conduction in its relation to the possible correction of conduction deafness. *J. Acoustical Soc. America* 8:112-117, 1936.
2. Lurie, M. H. What is perception deafness from a physiological and histological basis? *Ann. Otol., Rhin. & Laryng.* 48:13-16, 1939.
3. *Idem.* Studies of acquired and inherited deafness in animals. *J. Acoustical Soc. America* 11:420-426, 1940.
4. Selfridge, G. Nicotinic acid and the eighth nerve: a preliminary report. *Ann. Otol., Rhin. & Laryng.* 48:39-53, 1939. The eighth nerve in relation to thiamin chloride and nicotinic acid: a comparative study. *Ibid.* 48:419-432, 1939. Eighth nerve high tone deafness from a nutritional standpoint. *Ibid.* 48:608-631, 1939.
5. Mellanby, E. The experimental production of deafness in young animals by diet. *Laryngoscope* 49:1090-1118, 1939.
6. Covell, W. P., and Noble, L. The significance of myelin sheath degeneration for the cochlear nerve. *Ann. Otol., Rhin. & Laryng.* 46:895-911, 1937.
7. Covell, W. P. Pathologic changes in the peripheral auditory mechanism due to avitaminoses (A, B complex, C, D and E). *Laryngoscope* 50:632-647, 1940.
8. Lurie, M. H. The waltzing (circling) guinea pig. *Ann. Otol., Rhin. & Laryng.* 50:113-128, 1941.
9. Jones, R. C., Stevens, S. S., and Lurie, M. H. Three mechanisms of hearing by electrical stimulation. *J. Acoustical Soc. America* 12:281-290, 1942.

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTE-MORTEM AND POST-MORTEM RECORDS AS USED  
IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

### CASE 28221

#### PRESENTATION OF CASE

A fifty-eight-year-old housewife was admitted to the hospital because of abdominal pain.

In the seven weeks preceding entry, the patient had three episodes of pain and distress in the right upper abdomen associated with nausea and vomiting. Each attack came on rapidly at about three o'clock in the morning following a meal that included "rich foods." Each attack lasted about a day and left the patient feeling very weak. The pain was not cramping and did not radiate. There were no chills, fever or jaundice. The vomitus was never bloody or like coffee grounds. Fourteen hours before entry, the patient was awakened by severe, steady pain in the right upper abdomen and epigastrium. She felt nauseated, and vomited. There was much abdominal distention, some of which was relieved by the passage of gas by rectum. The abdominal pain continued unabated, and at the time of entry there was some pain in the right shoulder. On the morning of entry, the patient had a chill. The bowel movement on the day before the attack was "darker" than usual, although not bloody or tarry. The patient was usually constipated.

Twenty-five years before entry, she had an appendectomy. Twelve years later, she had several attacks of fainting and coughing, with slight hematemesis. A physician took roentgenograms and told the patient that she had "ulcers." She went on a Sippy diet and had no further complaints except for intolerance to fatty foods.

On admission, the patient appeared ill and pale. The heart was within upper limits of normal size. The lungs seemed clear. Deep respiration was painful. The abdomen was slightly distended, without apparent peristalsis. There was tenderness without spasm throughout the abdomen centering in the right upper quadrant. No masses were palpable.

The blood pressure was 122 systolic, 60 diastolic. The temperature was 99.5°F., the pulse 80, and the respirations 18.

Examination of the blood showed a white-cell count of 19,600. The blood Hinton reaction was negative. The urine was normal.

On the first hospital day, an operation was performed.

#### DIFFERENTIAL DIAGNOSIS

DR. RICHARD H. SWEET: Attacks of pain such as this patient had coming on at three o'clock in the morning after an evening meal of rich foods are likely to be caused by gallstones.

The temperature of 99.5°F., the pulse of 80 and the respiratory rate of 18 seem inconsistent with the statement that "the patient appeared ill and pale." At any rate, there was no shock.

From the past history, one can say with reasonable certainty that the patient had gallstones. On the other hand, a predominating factor in all the attacks was nausea and vomiting. In uncomplicated cholelithiasis, that is not common. When nausea and vomiting occur, one should suspect some complication of stones, such as cholecystitis or pancreatitis. The late Dr. Daniel F. Jones used to say that patients with gallstones rarely vomit. In spite of this, I shall assume from the past history that the patient did have gallstones.

I should like to exclude ulcer in this case in spite of the fact that an x-ray diagnosis of ulcer was made thirteen years before entry. There is very little to suggest ulcer to me unless we were dealing with an acute perforation. It is reasonable to assume that there was no acute perforation because the patient was apparently not sick enough. There was tenderness, but no spasm. Widespread tenderness without spasm is certainly not consistent with peritonitis.

I assume that she had gallstones with some complication. One must bring out certain points about the history to decide what the complication might have been. It is impressive that the pain was steady and very severe, and yet the patient was not very ill, according to the record. Could she therefore have had acute cholecystitis? The majority of patients with acute cholecystitis in my experience are apt to have rather higher temperatures when we first see them and often have higher white-cell counts: 19,600 is a high count, but acute cholecystitis is often associated with a count of 30,000 or more. The patient may have had acute cholecystitis, but I doubt it.

What else might she have had? Acute pancreatitis must be considered, especially as a complication in cases of gallstones. Acute pancreatitis alone would not explain the repeated attacks for a period of three months, but she might have had stones and then a final attack of pancreatitis. At any rate, the steady pain, the excessive nausea and vomiting, the pain in the shoulder on deep inspiration, the elevated white-cell count and the chill, which occurred not at the onset of symptoms but some time afterward, suggest it.

In this particular case, it is a difficult matter to differentiate cholecystitis and acute pancreatitis

complicating gallstones. If we take the physical examination as it reads, I presume that we must exclude pancreatitis because no mention is made of tenderness in the left upper quadrant; it is all in the right upper quadrant. The pain in the shoulder was also on the right side. However, I should not be at all surprised if she did have acute pancreatitis for the reasons that I have mentioned. It is because of nothing more than the clinical picture that I should lay more emphasis on pancreatitis than on acute cholecystitis. An observation that would have been of great value in differentiating such a case seen early after the onset would have been a serum or urinary amylase determination, or both. In early cases of acute pancreatitis, it has been helpful in some patients. I am reasonably certain that the surgeon who operated on this patient did not believe it was pancreatitis. We have learned, of late years, the disadvantages of early operation in cases of this sort, but I should not be at all surprised if that is what she had in addition to gallstones. I do not believe she had cholecystitis.

#### CLINICAL DIAGNOSIS

Peritonitis, probably due to perforated gall bladder.

#### DR. SWEET'S DIAGNOSES

Cholelithiasis.

Acute pancreatitis.

#### ANATOMICAL DIAGNOSES

Foreign-body perforation of ileum.

General peritonitis.

#### PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: I am afraid that the description of the abdominal findings as given in the abstract must be very inadequate, since the preoperative diagnosis was rupture of the gall bladder and general peritonitis. I shall ask Dr. Allen to take up the story.

DR. ARTHUR W. ALLEN: The patient had had repeated attacks of acute abdominal pain for several months, and her physician was so convinced that these were attacks of gallstone colic that he had had two Graham tests performed outside. The clinical story was not too convincing, but we believed that the acute episode was probably associated with the gall bladder. We thought of acute perforation because there was too much generalized spasm and tenderness in the abdomen to be accounted for on the basis of simple acute cholecystitis, and we operated under the diagnosis of perforated gall bladder with peritonitis. At operation, it was obvious that the gall bladder and

everything in the upper gastrointestinal tract were normal — no perforation of an ulcer or of the gall bladder, which looked normal and contained no stones. We encountered, however, some thin pus and thought we must find out where it came from. We could not ignore the fact that it was there, and we therefore proceeded in a systematic fashion to look over the intestine; about midway in the ileum, we encountered a tiny perforation, a foreign body — a chicken bone — lying quite close to it. It was easy to poke it through the hole it had made in the intestine. But, of course, one could never make that diagnosis beforehand without roentgenograms, and we had not bothered to have them made. We did examine the foreign body by x-ray afterward, however, and if we had had a film before operation we probably should have had a better lead. My next bet was Meckel's diverticulum, without any thought of foreign body.

The patient had no recollection of having swallowed the chicken bone, but this must have occurred several months before; without any question, the bone was responsible for some of her previous attacks, since it pricked here and there on the way down.

DR. MALLORY: Here is the postoperative x-ray film of the chicken bone. The patient made an extraordinarily quick and uneventful recovery, the chart becoming flat within two days, despite the obvious generalized peritonitis found at operation.

#### CASE 28222

#### PRESENTATION OF CASE

A seventy-five-year-old woman was admitted to the hospital because of abdominal pain of several hours' duration.

She was in good health until early on the morning of entry, when she was awakened by moderately severe pain in the abdomen to the left of the umbilicus. She arose, and bathed, but the pain grew gradually much worse and extended all over the abdomen, going through to the back and around the ribs. There was no true chest pain, but there was costal-margin pain with deep inspiration. Following onset of the pain, the patient took only a few sips of water, which she vomited. There was but slight nausea, and no subsequent vomiting. A normal bowel movement occurred in the morning. A physician found abdominal tenderness, with pain coming in waves. He sent the patient to the hospital.

In the fifty years before entry, the patient had rare episodes of pain resembling the last attack. Three years before entry, she consulted a physician because of this. At this time, roentgenologic examination of the upper and lower gastrointes-

tinal tract yielded no diagnosis. Subsequent to this examination, one or two attacks of similar character occurred, going away after a few days. Occasionally, the patient experienced transient sharp pain in the lower lateral part of the left chest when frightened. She had had no dyspnea or ankle edema. Twenty years before entry, a diagnostic curettage was performed for bleeding.

Examination showed an elderly woman who complained of pain moving across her abdomen in horizontal waves from a point to the left of the umbilicus. The abdomen was quite rigid, with generalized tenderness, and was rather dull to percussion, although it was obviously distended. High-pitched peristaltic sounds were audible over apparently undilated portions of bowel at the time of passage of a wave of pain. The lung fields were clear. The heart was not enlarged, and there was a soft apical systolic murmur. The pupils were of pinpoint size.

The blood pressure was 170 systolic, 90 diastolic. The temperature was 97.5°F., the pulse 85, and the respirations 15.

Examination of the blood showed a white-cell count of 7400 with 93 per cent polymorphonuclears, and a red-cell count of 6,250,000 with 90 per cent hemoglobin. The urine was normal. The serum amylase was reported as elevated.

A roentgenogram of the abdomen showed elevation of the diaphragm and poor aeration of both lower-lung fields. There was no evidence of free air beneath the diaphragm. A dilated loop of bowel consistent with either ileum or sigmoid lay in the left lower quadrant. No other definitely dilated loops of bowel were apparent.

The patient was given venoclyses of glucose in physiologic saline solution and morphine sedation. In the next eighteen hours, the temperature and pulse rose steadily to terminal levels of 103°F. and 130 respectively. The abdominal distention increased, and the patient failed rapidly. Death occurred about twenty-six hours after onset of the illness.

#### DIFFERENTIAL DIAGNOSIS

DR. CHAMP LYONS: The salient features of this case are the age of the patient and the catastrophic events that started in the left upper abdomen. Pain of sudden onset became progressively severe and radiated through to the back. Nausea and vomiting were present initially but soon disappeared. The pain was wavelike, and the abdomen was distended and spastic. The presence of mild shock is indicated by the subnormal temperature and probably by the elevated red-cell count. The life-endangering character of the difficulty is emphasized by the early death of the patient.

Gallstone colic and acute appendicitis with perforation are unlikely because of the onset of pain in the left abdomen. Rupture in an ectopic pregnancy is excluded by the age of the patient. Dissecting aortic aneurysm is an unlikely possibility with persistent urine formation. Three diagnoses must be seriously considered: perforation of a benign or malignant gastric lesion, high intestinal strangulation obstruction and acute pancreatic necrosis. The colicky pain, the absence of air under the diaphragm, the absence of gas in the jejunum, the character of the peristaltic sounds and the elevated serum amylase suggest that acute pancreatic necrosis is the proper diagnosis. The low leukocyte count and the history of previous rare attacks of similar pain are characteristic.

Acute pancreatic necrosis is hemorrhagic at its inception. If death follows after three or four days, the pathologist usually finds a gangrenous pancreas, and if the patient succumbs at a much later date, the pancreas may be suppurative. *Clostridium welchii* is frequently present on culture. I believe that this pancreas was hemorrhagic, with evidence of retroperitoneal dissection of serosanguineous exudate containing *Cl. welchii*.

The etiology of pancreatic necrosis is variable. The main factors are direct trauma, vascular injury, infection and bile invasion. Biliary-tract disease is concomitant in about 60 per cent of the patients, but there was no history of biliary colic in this patient, and a previous x-ray examination of the upper intestinal tract was reported negative. The onset of the pain was in the early morning and not after a full meal. Hence, bile reflux seems an unlikely cause of this pancreatic disorder, although the history of rare attacks of pain for fifty years is consistent with a biliary etiology. There is nothing to suggest a traumatic or infectious etiology. The patient's age indicates the existence of arteriosclerosis, and I believe that a vascular accident is the most likely cause of the acute pancreatic necrosis.

DR. ALLEN G. BRAILEY: I should like to ask Dr. Lyons how he fits the presence of a dilated loop of bowel and cramplike peristalsis into this picture.

DR. LYONS: We are not sure that the gas was not in the sigmoid, and this acute episode starting in the left upper abdomen ought to have produced high jejunal strangulation, not lower ileal obstruction.

DR. TRACY B. MALLORY: Why should the pain of pancreatitis be crampy, however?

DR. LYONS: I do not know, but it is. There are two theories about it: one is that the celiac axis is involved in the inflammatory process, and the other is related to the persistent swelling of the capsule. I discount the capsule theory but am willing to accept the celiac-axis suggestion.

DR. RICHARD H. SWEET: It is very common to confuse the diagnosis of acute pancreatitis and acute small-bowel obstruction, and it is difficult to differentiate them. One point that I have always considered helpful is that the patients with pancreatitis have a steady, intense pain in the back.

DR. BENJAMIN CASTLEMAN: How about the white-cell count?

DR. LYONS: It is characteristically low in acute pancreatitis.

#### CLINICAL DIAGNOSIS

Acute pancreatitis?

#### DR. LYONS'S DIAGNOSES

Acute pancreatic necrosis, hemorrhagic, probably secondary to thrombosis or embolism of pancreas.

Peritonitis, acute (*Cl. welchii*).

#### ANATOMICAL DIAGNOSES

Acute hemorrhagic pancreatitis.

Cholecystitis, chronic.

Cholelithiasis, probable.

Peritonitis, acute (*Cl. welchii*).

Thrombosis of splenic vein.

Pneumoperitoneum.

Pneumohydrothorax, bilateral.

Arteriosclerosis, aortic and coronary, marked.

#### PATHOLOGICAL DISCUSSION

DR. MALLORY: Post-mortem examination did show acute hemorrhagic pancreatitis in the distal half of the pancreas. The process had involved the splenic vein, which showed complete but fresh thrombosis, and there was not as yet necrosis of the spleen. Dr. Lyons prophesied that we might well obtain a positive culture for *Cl. welchii*. There was more obvious evidence of *Cl. welchii* infection, since gas gushed from the peritoneal cavity on our primary incision, and the liver and the spleen and some of the other tissues were grossly crepitant.

So far as the etiology is concerned, we have nothing positive to contribute. The patient did,

as most of these patients do, have severe biliary-tract disease. The gall bladder was small, firm and very fibrous, almost imbedded within the liver; it contained neither bile nor stones. The remaining biliary tract showed marked dilatation, with thickened walls and evidence of very longstanding chronic infection. Again, no stones were present in the ducts, but a small pigment stone that was found lying free in the duodenum may well have been squeezed out of the duct in our preliminary manipulations. Unquestionably, the patient had had severe infection of the biliary tract for several years. We did not make out any involvement of the celiac axis; she had moderate arteriosclerosis, which was not directly connected with this lesion.

DR. FLETCHER H. COLBY: Could the lesion have been due to bile reflux?

DR. LYONS: It is not likely that bile reflux caused the distal end of the pancreas to become necrotic.

DR. COLBY: How do you account for the *Cl. welchii*?

DR. LYONS: Dr. Lester Dragstedt\* has written an article on the pancreas in which he emphasizes the fact that *Cl. welchii* is important in this whole problem. His evidence is very good from an experimental point of view, and I think perhaps we have not paid enough clinical attention to it. I do not believe that the Welch exotoxin, which is extremely hemolytic, could have been active in this woman, since she had a red-cell count of over 6,000,000. I do not believe it was toxemia, or that treatment with *Cl. welchii* antitoxin would have been worth while. I am inclined to believe that this toxemia was the result of some action of the Welch bacillus on the pancreatic cells or a result of some bacterial poison that is a chemical constituent of the Welch bacillus itself. We do not know what it is, but it is almost universally associated with pancreatitis.

DR. COLBY: Where does the Welch bacillus come from?

DR. LYONS: It is always in the intestinal tract.

\*Dragstedt, L. R., Haymond, H. E., and Ellis, J. C. Pathogenesis of acute pancreatitis (acute pancreatic necrosis). *Arch. Surg.* 28:232-291, 1934

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established in 1828

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND  
PUBLISHED UNDER THE JURISDICTION OF THE  
COMMITTEE ON PUBLICATIONS

Official Organ of  
THE MASSACHUSETTS MEDICAL SOCIETY  
and  
THE NEW HAMPSHIRE MEDICAL SOCIETY

## EDITORIAL BOARD

Joseph Garland M.D.	Stephen Rushmore M.D.
William B. Breed M.D.	Henry R. Vetter M.D.
George R. Minor M.D.	Robert M. Green M.D.
Frank H. Lahey M.D.	Charles C. Lund M.D.
Shields Warren M.D.	John F. Fulton M.D.
George L. Tobey Jr. M.D.	A. Warren Stearns M.D.
C. Guy Lane M.D.	Dwight O. Hare M.D.
William A. Rogers M.D.	Ches. S. Keeler M.D.

## ASSOCIATE EDITORS

Thomas H. Ladd M.D.	Donald Munro M.D.
Henry Jackson Jr. M.D.	

Walter P. Boers M.D.	EDITOR EMERITUS
Robert N. Nye M.D.	MANAGING EDITOR
Clara D. Davis	ASSISTANT EDITOR

the next meeting of the General Court was unfortunate, particularly in view of favorable action on similar bills by the legislatures of certain other states, the sale of such drugs, however, is partially under federal control

According to Section 502 (f) of the Federal Food, Drug and Cosmetic Act,<sup>2</sup> a drug is considered to be misbranded "unless its labeling bears adequate directions for use." However, since Section 502 (f) states that a drug shall be deemed to be misbranded "if it is dangerous to health when used in the dosage, or with the frequency or duration prescribed, recommended or suggested in the labeling thereof," and since the Food and Drug Administration<sup>3</sup> has stated as its opinion that the barbiturates are included among drug products that are too dangerous for indiscriminate use, even if sold with labeling attempting to give adequate directions for use," most manufacturers are taking advantage of the exemption granted in the regulation of Section 502 (f) — namely, that the drug may be distributed if its label bears the statement, "Caution To be used only by or on the prescription of a physician."

Hence, the inspectors of the Food and Drug Administration are empowered to report any interstate shipment of a barbiturate — interstate shipment is believed to exist until the product is in the hands of the consumer — that does not bear on its label the above statement, in addition to the statement, "Warning May be habit forming, required by Section 502 (d)." Obviously, a retail druggist who dispenses a barbiturate in a container that is not properly labeled may be prosecuted, furthermore, the broader interpretation of the regulations prohibits the sale, other than on prescription, of such drugs, even in containers that are not misbranded. For the past year, the federal inspectors have conducted cross section investigations to determine the extent to which these requirements are being observed by the retail druggists, and although only one legal action has been brought on the basis of improper retail sales, further proceedings will be inaugurated if such sales continue. Of course, the Food and Drug Admin

SUBSCRIPTION TERMS: \$6.00 per year in advance postage paid for the U.S. and possessions; \$3.50 per year; Canada \$7.04 per year; foreign funds \$8.52 per year for all foreign countries belonging to the Postal Union.

MATERIAL for early publication should be received not later than noon on Friday.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the New England Journal of Medicine, 8 Fenway Boston, Massachusetts.

## REGULATION OF SALE OF BARBITURATES

A RECENT study<sup>1</sup> by a committee of the Connecticut State Medical Society gives ample proof of the conviction that the promiscuous use of barbiturates should be a matter of public concern and that these drugs should be sold only on prescription. That the same sentiment is held by the physicians in Massachusetts is evidenced by the fact that a recent legislative bill to limit the retail sale of barbituric acid, its derivatives and certain other sedatives to those possessing prescriptions from duly registered physicians, dentists and veterinarians was supported by the Massachusetts Medical Society. For this bill to be postponed to



istration has no control over products manufactured and sold within Massachusetts.

At least some advance has been made toward prohibiting the over-the-counter sale of barbiturates, and the legislatures of all states should create statutes, conforming with the regulations of the Food, Drug and Cosmetic Act, that will completely eradicate the evil.

### REFERENCES

1. Committee on Drug Addiction, Connecticut State Medical Society. Barbiturate addiction. *Conn. State Med. Jour.* 6:124, 1942.
2. *Federal Food, Drug and Cosmetic Act and General Regulations for Its Enforcement.* Service and Regulatory Announcements (Food, Drug and Cosmetic No. 1), Food and Drug Administration, Department of Agriculture Washington, D. C.: Government Printing Office, 1939.
3. Release by Food and Drug Administration, Federal Security Agency, dated April 24, 1941.

### PULSE—AND THE FUTURE

WITH an ever-increasing percentage of recent medical graduates called to the colors, a correspondingly greater burden falls on those too old for active military service and on those still in that period of training without which they would be of little use—as physicians—either in civilian or in military life. The former group has had experience, dulled a little, perhaps, by advancing years, but it is on the younger men that much of the burden of the present war must necessarily fall, although too many of them seem unaware of this trenchant fact. Plans for and visions of the future should not and must not come entirely from the older group. No matter what the fortunes of the next few years, a new era is being opened up, of which the mainstay will patently be the youth of today: the medical student of 1942 is the army officer of tomorrow. It is but just and proper, therefore, that their views—whether right or wrong—be publicized in some material manner. Since this country is fighting for democracy, a democracy to fight for must exist.

*Pulse*, which is the official publication of the New England section of the Association of Internes and Medical Students, expresses the views of one portion of the medical youth of America, and there is reason to believe that there are nonmembers who hold similar views. Some, of course, do not

agree; and hereon rests the responsibility of the editors of the publication: they must be rigorous in their efforts to represent truly the constituency under whose name they have chosen to promote themselves.

What are the purposes of this organization? It aims to serve the best interests of medical students and interns, wherever they may be, and to maintain and advance the ideals of the medical profession, thus serving society in general without respect to race, creed or color. More specifically, now that the United States is at war, this association aims to rally every medical student to an all-out war effort, to aid civilian defense by the training of Red Cross crews and catastrophe squads, to furnish, so far as possible, medical aid to the United Nations and to investigate what immediate changes might profitably be made in the curriculums of medical schools, so that these courses of study may be drawn more closely into line with the needs emerging from the present crisis. The members further wish to help in assuring that internships are of maximal educational value now that but one year is guaranteed and further training—except for service in the Army or Navy—is difficult to obtain.

In the April issue of *Pulse* appears an illuminating analysis of the financial needs of medical students under the new twelve-month medical-school system. One has, in a vague way, been aware that financial hardships must inevitably fall on some students under the new system, and although the constituted authorities are making every effort to avoid undue hardships, the average physician—who might be of help in one way or another—has not been apprised of the true state of affairs. The article is well worth study by all who are interested in the future of medicine.

*Pulse* is distributed as widely as circumstances permit among medical students, interns and physicians, and its columns are open to contributions as are those of any other periodical. Those who desire to obtain copies or to submit short articles should address their letters to 368 Longwood Avenue, Boston.

## MEDICAL EPONYM

## PARRY'S DISEASE

Sir William Osler considered that if any name should be attached to the syndrome of exophthalmic goiter, it should be that of Caleb Hillier Parry (1755-1822), M.D., F.R.S., whose description was published posthumously by his son in *Collections from the Unpublished Medical Writings of the Late Caleb Hillier Parry* (London, 1825; Vol. 2, p. 111). The condition is described under the general heading, "Diseases of the Heart":

*Enlargement of the Thyroid Gland in Connection with Enlargement or Palpitation of the Heart.* There is one malady which I have in five years seen coincident with what appeared to be enlargement of the heart, and which, so far as I know, has not been noticed, in that connection, by medical writers. The malady to which I allude is enlargement of the thyroid-gland.

This introduction is followed by the report of 8 cases showing a thyroid tumor with symptoms of tachycardia, exophthalmos and edema (1 case), of 7 cases of swelling of the thyroid gland with tachycardia or palpitation and of 5 cases of thyroid enlargement without heart symptoms.

R. W. B.

## MASSACHUSETTS MEDICAL SOCIETY

## COMMITTEE ON MATERNAL WELFARE

CASE HISTORY: FATAL PERNICIOUS  
VOMITING IN PREGNANCY

A thirty-one-year-old primipara was sent to the hospital toward the end of the third month of pregnancy because of nausea and vomiting. The past history was irrelevant. Although the patient had been married sixteen years, this was her first pregnancy. Physical examination showed no abnormalities other than moderate dehydration and a pulse elevated to 100. The nausea began about the sixth week, and treatment at home had been instituted; since the patient did not improve, she was hospitalized. Administration of insulin, glucose, adrenocortical extract and transfusions resulted in marked improvement for a few days, and she was sent home. Ten days later, she returned to the hospital in extremis and died without surgical intervention.

Autopsy showed acute parenchymatous nephritis, acute degenerative hepatitis, congestion of the spleen and early degeneration of the adrenal glands.

*Comment.* Pernicious vomiting, and this was a true case of pernicious vomiting, should not result

in death. The patient should have been hospitalized earlier. The treatment at the hospital did result in improvement, but it was probably not sufficient to warrant discharge.

The modern treatment of pernicious vomiting in pregnancy consists of hospitalization, the cessation of all food by mouth for forty-eight hours, the use of intramuscular thiamine chloride and intravenous glucose, and sedation. If this treatment is begun before definite degenerative disease has developed, improvement is rapid and remarkable. Rarely do such cases reach the point where therapeutic abortion is indicated to save life. This patient did not have thiamine chloride, but she did have glucose and transfusions. It is very probable that religious beliefs prevented surgery.

There is no such thing as pernicious vomiting per se in pregnancy. Death in these cases is due to pure starvation, which results in acidosis and degenerative changes in the kidney and liver.

One cannot help believing that this death was entirely avoidable. Earlier hospitalization and the routine treatment would probably have resulted in recovery. Therapeutic abortion was apparently not considered. Patients not treated early enough may need therapeutic abortion to prevent death, but this procedure, when a case has been intelligently handled and hospitalized early, is practically never necessary.

## DEATHS

DELAHANTY — WILLIAM J. DELAHANTY, M.D., of Worcester, died May 10. He was in his eighty-fifth year.

A native of Fitchburg, Dr. Delahanty received his degree from Dartmouth Medical School in 1883. He was an incorporator and a member of the staff of St. Vincent's Hospital, and was on the staff of the Worcester City Hospital for more than fifty years. He was a trustee of the Worcester State Hospital, and was a fellow of the Massachusetts Medical Society and the American Medical Association.

FIELD — HENRY M. FIELD, M.D., of Norwood, died May 20. He was in his sixty-eighth year.

Dr. Field received his degree from Harvard Medical School in 1904. He was a member of the staff of the Norwood Hospital, and a fellow of the Massachusetts Medical Society and the American Medical Association.

His widow survives him.

O'LEARY — CORNELIUS J. O'LEARY, M.D., of Brighton, died May 20. He was in his fortieth year.

Born in Charlestown, Dr. O'Leary received his degree from Tufts College Medical School in 1933. He had been associate medical examiner for the northern district of Suffolk County for seven years and was a fellow of the American College of Surgeons, the Massachusetts Medical Society and the American Medical Association.

His widow and four children survive him.

## WAR ACTIVITIES

### CIVILIAN DEFENSE

#### NEW PUBLICATIONS

*Protection of Hospitals*, Bulletin No. 3 of the Medical Division of the United States Office of Civilian Defense, prepared in collaboration with a special committee of the American Hospital Association, has now come from the press in its official form. It was previously published in several hospital journals in order that the material could be used by hospitals at the earliest possible moment.

The bulletin discusses protection of hospitals against air raids under the following heads: protection of building fabric, patients and personnel; protection of glass; ventilation; protection against fire; rescue squads; air-raid shelters; blackout regulations; protection of utilities; facilities for care of casualties; unit system and reserve stocks; the ambulance entrance; morals; distribution of casualties to wards.

Diagrams show how sandbag barricades can be used for temporary reinforcement, how to protect windows against shattering of the glass without cutting off ventilation, and several methods of blacking out. There is a sketch suggesting how an ambulance entrance can be designed to eliminate unnecessary turns, and there are also designs for signs to guide ambulances in the blackout.

The section on protection of glass gives detailed instructions on materials that can be used and methods of applying them. Under "Protection against Fires," there is a description of the various types of incendiary bombs and of the approved methods of fighting them. The report emphasizes the importance of fire and evacuation drills.

Facilities especially needed for the care of war casualties are a special reception room, in which casualties may be examined to determine their condition and immediate treatment, operating rooms in protected parts of the hospital (lower floors or basement), decontamination station for gas casualties and ample provision for a mortuary.

*Volunteers in Health, Medical Care and Nursing* has been issued for use of executives in civilian defense volunteer offices and of executives of agencies using volunteer services in these fields. The pamphlet outlines qualifications and duties for the following activities: automobile drivers, blood donors, child-care assistants, first-aid teachers, home-nursing teachers, health-department assistants, hospital and clinic assistants, laboratory assistants, library assistants, medical social-service assistants, nurses' aides, nutritionist assistants, occupational-therapy assistants, physiotherapy assistants and sanitation assistants.

## MISCELLANY

### DANGERS OF INDIRECT CONTACT WITH TUBERCULOUS PATIENTS

As long ago as 1865, Villemin successfully passed the "virus" of tuberculosis from one animal to another. Twelve years later (five years before Koch's discovery of the tubercle bacillus), von Tappeiner caused dogs to develop tuberculosis by allowing them to inhale sputum from a consumptive patient. Although direct lip contact is today considered the most potent means of transferring tubercle bacilli from person to person, knowledge of the relative dangers of indirect contact with tuberculous lungs and their secretions is still incomplete. Three recently published papers give evidence of this and, at the same time, sharpen one's perception of the manner in which bacilli go from host to victim.

### THE OCCURRENCE OF TUBERCLE BACILLI ON BOOKS AND GAIMENTS HANDLED BY PATIENTS WITH OPEN TUBERCULOSIS

(Jacobs, M. A., and Petroff, S. A. *Quarterly Bull. Sea View Hosp.* 7:33-39, 1941.)

Books read by tuberculous patients probably are occasionally contaminated by sputum in the form of droplets expelled during coughing or speaking as the book is closely held to the face or at such a level that any droplets expelled may readily be deposited upon the paper. Also they may contaminate books by licking the thumb or finger when turning the pages. Transmission of infection to a second reader appears likeliest to occur when the recipient with moist thumb or finger handles the contaminated pages, supposedly harboring the bacilli.

There is a general agreement that large portions of the bacilli deposited on the pages become dry and nonviable after a short time. Kenwood and Dowe exposed papers to coughing patients and dried them for one month, after which the washings from the paper surfaces were inoculated into guinea pigs of which not a single animal developed tuberculosis. Other experiments of this kind point to the conclusion that although the risk of infection from books is not to be belittled, the possibility of transmission from such channels is extremely small.

Jacobs and Petroff permitted certain patients with advanced pulmonary tuberculosis, with uncontrollable cough and with sputum of Gaffky 6 to 8, to handle books carelessly as possible. They coughed on the marked pages, and wet their thumbs with saliva when turning the pages. Scrapings later derived from the marked pages were collected and suspended in physiologic saline solution. Tuberculin-negative guinea pigs were inoculated with this solution. Three of the 16 guinea pigs died from intercurrent disease, and no evidence of tuberculosis could be found at post-mortem examination. The other remained tuberculin negative ninety-two days after inoculation, when they were sacrificed.

Another set of experiments demonstrated that the droplets collected by scrapings from garments worn by patients with open tuberculosis did not infect guinea pigs. However, this failure should not give rise to a sense of false security and to a laxity of precautionary measures. The summary includes the following suggestions:

At present, the best way to ease the mind of the possibility of transmission by a book that has been handled by a patient with open tuberculosis is to store or quarantine the book for several weeks until the morbid material is completely dried, since it has been shown repeatedly that the drying robs the bacilli of their power of producing disease in animals. This measure was recommended by the British Joint Tuberculosis Commission.

There is no suggestion of importance concerning the patients' garments should be disinfected. Perhaps the safest way is to expose them to the sun and air for a few days before storing them away.

### SURVIVAL OF TUBERCLE BACILLI

(Smith, C. R. *Am. Rev. Tuberc.* 45:334-345, 1942.)

Cultures were made from swabbings of bedside tables, lamps, bed frames and other articles in rooms occupied by patients at Barlow Sanatorium, and from room dust sweepings and cotton filters through which room air had been sucked. Uniformly negative results led to speculation regarding the effect of daytime roomlight on living tubercle bacilli.

Review of the literature seems to sustain the statement

Park and Williams that "Tubercle bacilli in sputum when exposed to direct sunlight are killed in from a few minutes to several hours according to the thickness of the sputum and the season of the year. They are usually destroyed by diffuse daylight in from five to ten days. Dried sputum in rooms protected from abundant light has occasionally been found to contain virulent tubercle bacilli for as long as ten months."

For the present experiment, suspensions of virulent human tubercle bacilli in water or in sputum were spread on cover slips in 0.05-cc amounts and allowed to dry. Some of these preparations were placed in a small unheated room in the light of an unglazed but screened north window through which the sun was known never to shine, others were kept in complete darkness within a cardboard box inside a second such box, which in turn was kept in a table drawer of an unheated room. This was done during a clear, dry period in midwinter at Los Angeles.

A second set of tests was run in the early spring during cloudy and rainy weather, and a third set of tests in midsummer. The following winter, viability was also tested in the electric refrigerator.

The viability of tubercle bacilli was determined by animal inoculation and by culture.

Dried tubercle bacilli survived unfiltered north room light from four hours to five days under varying conditions. They were nonviable, according to the methods of recovery used, at one to twelve days, the viability was not established in one case.

Viability in the dark was from less than forty days to between three and a half and five months.

Viability in the refrigerator was between six and a half and fourteen months.

Tubercle bacilli were more readily recoverable and after longer periods of exposure when the dose deposited was larger. They lived longer in smears made from sputum than in those from water suspensions. They lived longer in the winter than in the spring and summer.

Variations in relative humidity and periods of partial cloudiness had no effect on viability.

Unfiltered daytime roomlight probably plays a very important role in preventing cross-infection and in protecting the employees of tuberculosis sanatoriums.

#### THE DISSEMINATION OF TUBERCLE BACILLI FROM FRESH AUTOPSY MATERIAL

(Sloan, R. A. *New York State J. Med.* 42 133, 1942)

Two incidents seem to have prompted this study: the isolation of acid fast organisms from the surface of eye glasses worn during an autopsy on an active case of tuberculosis, and the observation that the incidence of tuberculosis among medical students appears to be proportional to their contact with autopsy material during the second year in medical school. The compression of the crepitant lung, causing expulsion of minute amounts of bacterial laden air, might simulate a human cough and thus be responsible for the dissemination of bacteria.

Lungs from patients who died from tuberculosis were sectioned in the usual manner, the trachea was opened, regional lymph nodes were examined, and all cavities were opened with scissors. This was done under a shield, equipped with a glass plate situated about 20 cm. directly above the specimen. After a fifteen minute examining period, the plate was washed with sterile saline solution.

The growths obtained from the washings led to the conclusion that methods of examination that make use of a compression technique in atmosphere in

the vicinity of the autopsy, and that fresh tuberculous lungs are decidedly dangerous and are a potent source of atmospheric contamination, against which methods of proper protection should be devised.—Reprinted from *Tuberculosis Abstracts*, May, 1942

#### NOTES

Seven appointments to the teaching and research staffs of the Harvard Medical and Dental schools were recently announced by Harvard University as follows: John B. Hazard, MD Harvard '30, of Wellesley, assistant in pathology; Mark S. Donovan, MD University of Michigan '35, of Boston, assistant in roentgenology; Luke Gillespie, MD Harvard '37, of Windrop, assistant in obstetrics; Dario Azevedo, MD Faculty of Medicine, of Lima, Peru, '30, research fellow in physiology; Zenal Kiper, MPH Harvard '40, of Boston, research fellow in surgery; Francis Rouilland, MD Harvard '27, of Cambridge, assistant in obstetrics; and Richard D. Garrett, DMD Harvard '39, of Glens Falls New York, assistant in surgery.

Harvard University has recently announced the appointment of J. Howard Mueller, PhD, as professor of bacteriology and immunology at Harvard Medical School and School of Hygiene and Public Health, a position made vacant by the death of Dr. Hans Zinsser in September, 1940. Drs. Fuller Albright, Allan M. Butler and Hiram H. Merritt were promoted to associate professorships in medicine, pediatrics and neurology, respectively, and Dr. Frederick J. Stare, a graduate of the University of Chicago School of Medicine, was named assistant professor of nutrition.

At a recent meeting of the American Association of the History of Medicine, the William Osler Medal was awarded to John T. Barrett, 43, of Boston University School of Medicine.

Dr. Leopold F. King, of Lowell, was recently elected president of the Massachusetts Society of Examining Physicians. He succeeds Dr. Roger T. Doyle.

Dr. Walter B. Cannon, George Higginson Professor of Physiology at Harvard Medical School, has recently been made an honorary member of the Russian Academy of Sciences. Two other Americans and two Englishmen were similarly honored, this being the first time since the Russian revolution that such distinction has been granted to foreigners.

#### REPORTS OF MEETINGS

##### CARNEY HOSPITAL JOURNAL CLUB

At a regular monthly meeting of the Carney Hospital Journal Club at the hospital on January 8, Dr. Robert Wilkins, of the Evans Memorial Hospital, spoke on "Recent Developments in the Pathological Physiology of Hypertension." After briefly reviewing the fundamental work of Goldblatt, on which most experimental investigation in this field is now based, Dr. Wilkins discussed the types and characteristics of experimentally produced hypertension. The first general type is popularly known as that caused by "renal ischemia." This was originally effected by Goldblatt by applying a clamp on the renal artery and was later produced by the artificial constrictive perinephritis of Page's cellophane capsules. That any changes in such cases are not truly the result of anoxia of the kidney is now generally accepted, since experiments have

demonstrated that there is no decrease in the blood flow to such an organ. The significant change is apparently one from a pulsating to a steady type of blood flow.

The following facts are characteristic of such hypertension. It is cured by removal of the involved kidney. The blood pressure may not immediately return to normal, apparently depending on the duration and degree of the hypertension. This is probably associated with its effect on the other kidney. Wilson and his co-workers have shown that the clamp keeps the elevated blood pressure from affecting that kidney, whereas the normal organ is adversely affected. Hypertension is increased if the normal kidney is removed; this indicates that the latter in some manner protects the animal. The onset of hypertension is not prevented, nor is its course altered by renal denervation, complete sympathectomy or pithing; this type of experimental hypertension has no relation to renal innervation and is probably humoral in its mechanism.

The second general type of experimental hypertension is the so-called "neurogenic" kind, which is produced by removal of the carotid sinuses and the depressor nerves (Heyman's operation) or by artificial increase of the intracranial pressure (Cushing). The characteristics of this type are its lability, its abolition by pithing or complete sympathectomy, and its failure to be eliminated if only the renal (adrenal) or the cardiac innervation is intact. This, then, is essentially a nervous mechanism as compared with the humoral character of the other type.

The relation of such hypertension to the human form is borne out by the fact that at least certain cases in man seem to have some degree of "renal ischemia." Furthermore, splanchnic sympathectomy has a definitely beneficial effect in certain cases. And since this operation removes both the renal and adrenal innervation, it is conceivable that the kidney is a common factor. In further support of this hypothesis are the observations that in hypertensive patients there is a vasoconstriction of the efferent renal arterioles, as demonstrated by Smith's Diodrast-clearance and inulin-clearance tests, and that the blood of such patients is more vasoconstrictive than that from normal controls (Page).

Another problem is the character of "renin," a substance that is obtained from kidneys and is the precursor of angiotonin and hypertensin, which are now being employed to produce experimental hypertension. Earlier preparations of this compound were apparently impure, for they caused a depressor effect after the pressor. It has now been demonstrated that this substance is a protein, is heat labile, and combines with a pseudoglobulin to produce angiotonin, the last reaction being dependent on the temperature, the time and the proportion of reacting substances. All these are, of course, characteristics of an enzyme. Angiotonin (hypertensin), on the other hand, is a protein that is heat stable, dialyzable and crystallizable, and is destroyed by an excess of renin or tissue extracts. Therefore, it is a relatively pure substance but is not an enzyme.

The crucial experiment attempted by Dr. Wilkins and his co-workers was to determine whether angiotonin causes human hypertension of the proper pattern. For this purpose, they used themselves as subjects and employed angiotonin supplied by Page. It was concluded that this substance does cause a characteristic and marked hypertension, without any significant side effects, in the majority of subjects. There is often dizziness at the onset, and some subjects later experienced substernal oppression and palpitation. One doctor complained of severe headache closely resembling that of hypertension.

This indicates that these symptoms, so often clinically attributed to a superimposed "neurosis," are in reality the result of the high blood pressure. There was a significant rise in the blood pressure (190 systolic, 120 diastolic). Bradycardia, a constant finding, could be abolished by atropine, whereas the hypertension was heightened. The venous pressure, surprisingly, rose to failure levels, with visible neck veins in certain cases. There was a concomitant decrease in vital capacity. The cardiac output, as suggested by Starr, was sharply diminished. This is the only pressor substance that acts in this way, according to this observer, who has reported that adrenalin, amphetamine (Benzedrine) and so forth either do not change the output appreciably or increase it. These findings suggested the similarity to cardiac failure, and this was borne out further by teleoroentgenograms and chest plates, which revealed increased lung markings or enlargement of the cardiac shadow, or both. That there is peripheral vasoconstriction was corroborated by skin temperatures and plethysmographs. That angiotonin is a true vasoconstrictor independent of the sympathetic nervous system was proved by its action in the absence of this system and when injected intra-arterially and at skin temperature to the part measured. It does not overcome sympathetic control, however. Whether the hypertension resulting from angiotonin is the same as the naturally occurring disease depends on how one wants to interpret the evidence, for there are some facts in favor of both views. The lack of any increase in venous pressure in the human disease, unless there is cardiac failure, is in contrast to the experimental facts, but the cardiac failure is an acute episode. The spasm of the renal efferent arterioles is found in both conditions. Page and Houssay both hold the opinion that the substance causing human hypertension is either similar to or the same as angiotonin (hypertensin).

Since the presence of a normal kidney acts as a protection against both types of hypertension, there have been numerous attempts to find depressor substances in normal kidneys to counteract the pressor material from abnormal renal tissue. Such depressors act only if there is a high blood pressure. In all the outstanding laboratories, there are now such materials, which decrease the hypertension in animals and in certain human subjects. Since there are many severe reactions at first, Page has so far employed his depressor only in very advanced cases and in practically moribund patients. Nevertheless, he is firmly convinced that he is gradually obtaining a purer substance and that the reduction of blood pressure is not attributable to the side reactions of shock, fever or toxic manifestations, as some observers maintain. In favor of his contention is the slow and prolonged reduction of blood pressure, in contrast to the precipitous fall in toxic reactions and shock. Furthermore, there have been satisfactory results in some patients without side reactions, whereas some of those with the severest toxic manifestations revealed no fall in pressure. The hypertension returns if this therapy is not continued. All the measurable signs, such as increased cardiac output, decreased venous pressure and efferent arteriolar dilatation, testify to the efficacy of this "antiangiotonin."

Schroeder, in New York, working from the chemical standpoint that all these compounds have the basic structure of tyrosinase, has used this substance to render angiotonin inactive *in vitro*. It definitely decreases the hypertension in experimental rats, but its use in human beings is not advocated. It was advanced as a method of investigation, and is too difficult technically to be used in man.

Another form of therapy of human hypertension that has met with success in some cases in the hands of certain

surgeons such as Peet and Smithwick, is sympathectomy. The question arises whether it is merely palliative and non-specific but there is no doubt of its efficacy in properly selected cases. It should be noted that there is no measurable increase of renal blood flow after this operation. In considering human hypertension in general, one should realize that it is not a simple problem, for apparently civilization adds some conditioning factor, as evidenced by the lack of this syndrome in the Australian aborigines and in Negroes in their native African countries. Whether this indicates the presence of a neurogenic factor is still a moot point.

In answer to questions, Dr Wilkins pointed out that such therapy as might result from the introduction of a gonitoin inhibitors will probably have to be periodic and continuous like insulin. In certain cases in which a cycle is present, it might be possible to break in and thus allow smaller doses or less frequent administration of the material. The strong heredity factor and neurogenic pattern in human hypertension are corroborated by previous tests of any type (immersion of hands in cold water) which demonstrate that hypertensive patients show a stronger reaction and that there is a higher percentage of future hypertensive patients in present hyper reactors and their children than in those showing a normal response.

#### NEW ENGLAND PATHOLOGICAL SOCIETY

A regular meeting of the New England Pathological Society was held on January 15 at the Evans Memorial Massachusetts Memorial Hospitals. Dr B Earle Clark presided.

The first paper, Experimental Allergic Inflammation of the Intestine was presented by Dr George Hartley. Previous work suggested that ingested antigen is localized in the intestinal wall by specific antibodies. Because the work of Opie and others has shown that allergic inflammation in the skin (the Arthus phenomenon) is caused by a localization of antigen by antibodies, the demonstration of such a reaction in the intestine would prove that antigen is localized by antibodies in this organ. Following the injection of crystalline egg albumen into the rectum or directly into the wall of the cecum of hypersensitive rabbits, a severe inflammatory reaction developed locally. A similar inflammatory response was produced in the ileum of hypersensitive rabbits following the injection of antigen into a small radicle of the mesenteric artery. The inflammation was characterized by a marked neutrophilic infiltration of the entire wall (mucosa, submucosa, muscularis and serosa), edema and slight hemorrhage of the submucosa, and vascular congestion of the submucosa and subserosa. Eosinophils in rabbits are difficult to distinguish from neutrophils but Dr Hartley believes that there was an infiltration of these cells as well as of the neutrophils, in the intestinal wall. At the site of the mesenteric arterial injections, acute arteritis and periarteritis developed. No lesions were present in the normal control rabbits that were treated in the same manner as the hypersensitive animals. All the lesions were present after twenty-four hours. Older lesions have not yet been studied. These experiments demonstrate for the first time the direct production of allergic ileitis. The resemblance of this allergic inflammation of the intestine in rabbits to acute appendicitis and the nonspecific inflammations of the small intestine in human beings suggest the possibility that some of these inflammatory reactions may be allergic. Finally, since it has been definitely established that allergic inflammation in the skin (the Arthus phenomenon)

is the result of the localization of antigen by antibodies, these experiments suggest that antigen is localized by specific antibodies in the intestinal wall.

In the discussion, it was questioned whether Dr Hartley had justified his conclusions. The fact that the histologic preparations of his experimental animals resembled appendicitis and ileitis was insufficient to prove that these diseases are allergic. Dr Alvin Moritz warned against giving too much emphasis to the eosinophil as evidence of an allergic state.

The next paper, Temporal Arteritis. Report of a case, was presented by Dr David Skinner. Biopsy of one temporal artery showed moderate thickening of all the coats, with preservation of the internal elastic membrane. The adventitia and portions of the media were replaced by old granulation tissue. The adventitia, media and intima were heavily infiltrated with endothelial lymphocytes, occasional plasma cells and very rare eosinophils, but no giant cells were observed.

In the discussion Dr Tracy B Mallory reported that he had seen 6 cases at the Massachusetts General Hospital. He brought out the point that the vessel changes can usually be distinguished from periarteritis nodosa microscopically but that occasional difficulty may be encountered in differentiating it from thromboangitis obliterans.

Another paper Spontaneous Renal Infarction in Infants was presented by Dr Skinner. During the last fourteen years 8 cases of renal infarction have been observed among 462 consecutive autopsies on infants one year old or younger exclusive of stillbirths. The infarct was bilateral in 7 cases total in 4, and partial in 2. Venous thrombi were present in 3 cases. Associated conditions were pneumonia in 5 cases, cleft palate with malnutrition in 2, acute enteritis in 2 and marasmus in 2. No definite cause for the infarction could be determined. The next paper Wilson's Disease. Report of a case, was presented by Dr Donald Nickerson. A twenty-five year-old woman was admitted to the hospital complaining of enlargement of the abdomen and pain in the left upper quadrant. The patient had been perfectly well until the age of fifteen, when she began to have irregularity of the menstrual periods, followed by complete amenorrhea nine years later. On examination, the outstanding finding was a very large spleen, which reached to the crest of the ilium, and a painful subcutaneous nodule just above the umbilicus. Neurologic examination showed no definite spasticity but a coarse shaking tremor of both hands, hyperactive knee and ankle jerks, no interference with sensorium and evidence suggesting cerebellar dysfunction. Laboratory examination showed a rather marked secondary anemia, with moderate achromia and poikilocytosis. Blood chemical studies, including cholesterol, calcium, phosphorus, phosphatase and total protein were essentially negative. The sedimentation rate was moderately active. The spinal fluid examination, blood and spinal fluid serologic findings, blood fragility studies and repeated Bence-Jones determinations on the urine were all negative. A x-ray examination showed marked splenomegaly and moderate demineralization of the skeleton. The patient who was discharged from the hospital with a diagnosis of Wilson's disease, progressed fairly well for nine months, during which time she had been studied in a Boston hospital, where the same diagnosis was made. The last admission was due to marked abdominal enlargement with edema of the ankles, for which paracenteses were done, on the sixth hospital day a fatal hemorrhage into the intestinal tract occurred. Post mortem examination showed an extreme cirrhosis of the liver, which weighed 675 gm and whose gross and

microscopic appearance was that of a healed acute yellow atrophy. The spleen was markedly enlarged, weighing 740 gm., and showed no gross lesion beyond extreme engorgement. There was a small, perforated, esophageal varix from which a fatal hemorrhage had occurred. Examination of the brain showed distortion of the relation of the left basal ganglia, and microscopic sections showed rather extensive gliosis in the left lenticular area.

In the discussion, Dr. Ernst E. Mathias suggested that Wilson's disease may be one of a group of diseases, the other members being Huntington's chorea, pseudosclerosis and athetosis.

The final paper, "The Mitotic Activity of a Group of Colchicine-like Compounds," was presented by Dr. Charles Branch. It has been established that colchicine is a toxic drug that has a profound effect on cell division. Several investigators have attempted to find a substitute or derivative of comparable activity but less toxicity. The present study was concerned with a group of twelve such compounds, tested for their effect on mitotic activity. For each experiment, 50 mice (Strain C57), planted with sarcoma (Strain 37), were used. The compound to be tested was injected in varying doses, and the mice were sacrificed at regular intervals, up to twenty-four hours. Compounds differing considerably in their chemical structure all produced mitotic showers comparable to colchicine, but were apparently less toxic than that drug. Several of the animals with varying sized tumors were displayed.

## BOOK REVIEWS

*School Health Services: A study of the programs developed by the Health Department in six Tennessee counties.* By W. Frank Walker, Dr.P.H., and Carolina R. Randolph. 8°, cloth, 197 pp., with 139 tables and 12 charts. New York: The Commonwealth Fund, 1941. \$1.50.

In view of the steady growth of school health services in this country and the relatively important place they occupy in the public-health program, a critical study of objectives and the results obtained is long overdue. The authors have attempted such a study in a group of Tennessee counties where school health work has been well organized for ten years, and where uniformity of both examinations made and records kept far exceeds the average.

The main objective is the appraisal of certain standard procedures in terms of pupil response. The dominant influence of the presence of the parent at the time of examination comes as no surprise. Nursing supervision alone had much less influence in securing the correction of defects, but was far from negligible. Although preschool health supervision definitely increased the percentage of immunization of children against diphtheria and typhoid fever, it showed no effect on the percentage vaccinated against smallpox. A satisfactory response in all three kinds of immunization followed school supervision.

Some of the questions raised by this study are perhaps more significant than the conclusions that could be drawn. How far can routine school examinations go without interfering with more productive activities in the public-health program, or even with the correction of defects found? One might also ask how far a health department should go with school procedures that involve personal rather than public health. In terms of results, are routine dental examinations justified unless the community can provide corrective treatment when needed?

The authors' clear style and concise statement will appeal to the general reader, and the public-health worker will find in the book a challenge to more objective think-

ing in a somewhat nebulous field. The printing and format of the book uphold the usual high standard of the Commonwealth Fund publications.

*A History of Medical Psychology.* By Gregory Zilboorg, M.D., in collaboration with George W. Henry, M.D. 8°, cloth, 606 pp., with 21 illustrations. New York: W. W. Norton and Company, Incorporated. \$5.00.

Nobody in America writes with more fluency than Gregory Zilboorg. As a leader in medical thinking he has brought to this country the best of the European tradition. This new volume on the history of medical psychology is not merely an account of what has happened but also a critical appraisal, intelligently organized and interestingly told. Up to the present time, no book more scholarly than this has appeared in English. How Dr. Zilboorg has been able to do it in the midst of his heavy work as a psychiatrist and psychoanalyst is explained in part by the fact that he has had the assistance of Dr. George W. Henry.

Although Dr. Zilboorg is himself a psychoanalyst, it cannot be said that this book suffers from psychoanalytic bias. It is written from the philosophic and humanitarian point of view. Only a physician with broad human contacts and vast learning could have produced this document, on which every physician can afford to look with pride.

This book is not for light reading, although there are many parts of it that are charming and amusing. Rather, it is a book for study and reference. It is a book one could keep on one's bedroom reading table, where in quiet and in reflection one could appreciate the scope and profundity of Dr. Zilboorg's labors.

Dr. Zilboorg points out several important facts that until now have not been adequately stressed. His emphasis on the neuroses (Chapter 9) and on "psychiatric revolutions" (Chapters 7 and 11) will guarantee the reader ample reward for reading these sections if he has not time to read the whole book.

Dr. Henry's separate contribution on mental hospitals (Chapter 14) is well worth reading, since the facts it contains should be common knowledge to every physician in America today.

*About Ourselves: A survey of human nature from the zoological viewpoint.* By James G. Needham, M.S., Ph.D. 4°, cloth, 276 pp., with 45 illustrations. Lancaster, Pennsylvania: The Jaques Cattell Press, 1941. \$3.00.

The complex story of the development of animals and man is retold in a simple, often humorous, way by the former professor of entomology at Cornell University. There are chapters on the primates, man's remote ancestry, the development of the nervous system, instinct, learning, infancy and similar topics. The material is presented in language that a young adult could understand; this is an oft-repeated story, but well done, as might be expected from a well-trained biologist.

The last half of the book deals with a larger problem—society in its biologic aspects. Here one touches medicine, government, war, folkways, social behavior and human affairs. One senses that the author is not so happy in this broader field; certainly, his knowledge of medicine leaves much to be desired. For example, he gives eight symptoms of hysteria, no one of which would be accepted by a physician as diagnostically significant (page 216).

It is difficult for the reviewer to decide for whom this book was written. A grade school or college underclassman might profit by Part 1; Part 2, for adults, seems of less value.

# The New England Journal of Medicine

Copyright, 1942, by the Massachusetts Medical Society

VOLUME 226

JUNE 4, 1942

NUMBER 23

## SOME REMARKS ON THERAPY FOR ANEMIA\*

WILLIAM B. CASTLE, M.D.†

BOSTON

I AM sincerely appreciative of the honor bestowed on me by the invitation to deliver this oration. As you are aware, my distinguished predecessors have annually instructed and entertained you with words both wise and charming. I wish, especially at this preprandial hour, that I were able to do so. Lacking such gifts, however, I have believed that in accepting this honor it would be a more suitable expression of appreciation were I to speak of matters of detail with which I have some experience than to discourse, perhaps naively, on a more general theme.

\* \* \*

The remarkable advances in the treatment of anemia of the past decade and a half, when contrasted with the yet unscalable obstacles, perhaps justify an attempt at a realistic appraisal of the possibilities and limitations of existing therapy. Today, five general methods of treatment of varying effectiveness and permanence are clearly discernible. Thus, there are substitution therapy for nutritional deficiency or for dysfunction of the endocrine system, chemotherapy, splenectomy and irradiation. Finally, on its own merits and also as a means of preparation for some other form of therapy, there is transfusion.

### SUBSTITUTION THERAPY

Starting with the pioneer clinical observations of Minot and Murphy in 1926, the effectiveness of liver and later of stomach preparations in the treatment of patients with nutritional types of microcytic anemia has become thoroughly established. In this locality, the conditions amenable to such therapy are usually Addisonian pernicious anemia and that of pregnancy. With the further exception of certain rare cases of nutritional macro-

cytic anemia, usually due to intestinal disturbances, all types of anemia fail entirely to respond to such preparations. Valuable contributions to the practical development of the present effective therapeutic products have been made by both university and commercial research groups. Since the amount of active material remaining in the finished product depends on the efficiency of the method of manufacture, it seems unwise and uneconomical for physicians to prescribe products whose potency is defined only in terms of the amounts of tissue with which the manufacturer started his process. The obvious and satisfactory alternative definition of potency in terms of the amount of effective material in the final product is currently described in U.S.P. units for all antianemia remedies accepted by the *United States Pharmacopoeia* or the Council on Pharmacy and Chemistry of the American Medical Association.

Active commercial preparations of the liver for oral or parenteral use, and of the stomach or of the stomach and the liver potentiated by incubation for oral use, are available. Because in the average patient the effectiveness of a given liver preparation is from sixty to one hundred times as great when given parenterally as when taken by mouth, the former route provides a distinctly more economical manner of administration. The small volume of material to be injected (several commercial preparations contain at least 15 U.S.P. units per cubic centimeter) and the infrequency of injections required for maintenance (15 or 30 U.S.P. units at intervals of two weeks or a month) render the use of any oral preparation a doubtful policy, from the point of view of both effectiveness of treatment and convenience or expense to the patient. Few patients conscientiously persist in taking considerable amounts of medicine by mouth two or three times a day for long periods after they consider themselves perfectly well. Because a definite but unpredictable num-

\*The Annual Oration delivered at the annual meeting of the Massachusetts Medical Society, Boston, May 26, 1942.

†Professor of medicine, Harvard Medical School; associate director, Thorne Electric Memorial Laboratory; director of Second and Fourth (Harvard) Medical Services, Boston City Hospital.



ber of patients in severe relapse fail more or less completely to respond to products administered orally in usual amounts, it is certainly unwise to initiate treatment by any other method than that of parenteral therapy, usually in terms of multiple *U.S.P.* units daily for the first few days. A similar indication is provided by patients with pronounced neural manifestations. With exceedingly rare exceptions, the present purified and concentrated preparations seem to be as effective as the older and cruder products in the treatment of pernicious anemia and its neural complications. A practical point in the early detection of the onset of remission is to determine the reticulocyte percentage on the fifth and seventh days after therapy with liver or stomach preparations has been instituted. In the response of anemic patients, the increase of the reticulocytes is so much more striking than the change in red-blood-cell or hemoglobin values in the first week that, relying only on the latter, the physician may fail to realize that the response has already begun.

Although liver extracts, especially the less highly purified products, are to some extent sources of various members of the vitamin B complex, these are apparently unessential to the remission induced by the active hematopoietic principles of liver. The treatment of pernicious anemia by vitamins is thus a waste of material. Whereas it is true that large amounts of whole or autolysed yeast may, under experimental conditions, cause detectable improvement in pernicious anemia, it is probable that these agents act only indirectly through their power to induce the formation of liver extract in the body. In actual practice, they are without significant value compared to the efficiency of active liver or stomach preparations, and their use is an additional burden on the patient and his pocketbook. Whether or not vitamin C is an effective agent in the rare macrocytic anemia of scurvy remains to be proved. Since fruit juice containing vitamin C has been shown to be capable of causing blood regeneration in such patients, it can be readily employed in any case whether its activity depends on ascorbic acid or other factors. Today, the sole essential for maintaining continued and complete remission in pernicious anemia is the exhibition of sufficient amounts of active material by a single route at regular intervals. The advances of the last fifteen years have almost deprived the adjective "pernicious" of any real meaning. Indeed, it is a puzzling question whether the diagnosis "pernicious anemia" should appear on the death certificate of a patient who by adequate treatment has been maintained through many years with a normal blood count and who has died of causes entirely unrelated to his original anemia.

The effective use of iron in the treatment of anemias now known to be hypochromic is older than the record of history. Its latest and presumably permanent reappearance on the platform of sound therapy dates from the independent observations of Barkan and Meulengracht, in 1923, in Europe. They abandoned the small amounts of iron advised by theory and used dosages comparable to those effectively employed today. It is now known that almost any sort of iron, if orally administered in a finely divided form or as a nonirritating iron salt, is effective in the treatment of hypochromic anemias in which loss of hemoglobin and consequently of iron has been brought about by bleeding, pregnancy or growth. Observation shows that ferrous compounds are in general more effective than ferric. The dosage of ferrous compounds is about 5 gr. three times a day, best given just after meals to avoid gastric irritation. Many injections of iron have been made without much effect because of the minute amount of iron in these often expensive and elegant ampules. Today, it is recognized that it is very rarely necessary to promote hemoglobin regeneration by injections of iron. If, however, because of failure of oral therapy in adequate dosage, such a procedure is required, suitable preparations—sterile solutions of ferric ammonium citrate or ferrous gluconate—are available.

The indication for the use of iron is a low hemoglobin concentration in the red blood cells or a low color index. Unfortunately, the hypochromic anemia of chronic infections and that of the so-called "Mediterranean anemia," although possessing these characteristics, do not respond to iron. Experimental animals with hypochromic anemia that have failed to respond to iron are often relieved by vitamin B<sub>6</sub>, but this is not true of patients, at least in my experience. In growing experimental animals, carefully deprived of access to copper, it has been convincingly shown that this element as well as iron is essential for relief of the anemia that develops. Some authors have reported a similar use for copper in anemic infants given small doses of iron. There is, however, no convincing evidence that patients failing to respond to usual doses of iron will respond to the addition of copper. Liver and stomach preparations are useless. Moreover, indiscriminating polypharmacy obscures the effective agent and may lead to needless and expensive types of maintenance therapy. Iron, therefore, appears to be the only agent of practical importance in the treatment of hypochromic anemia.

Patients with myxedema commonly have some degree of hypochromic and occasionally macrocytic anemia, especially if gastric anacidity is pres-

it. Hypopituitary syndromes are also sometimes associated with anemia. Treatment in both conditions depends on suitable endocrine therapy, and may be accelerated by the use of liver extract or oil, according to the character of the anemia.

### CHEMOTHERAPY

Chemotherapy, although primarily employed for the infection itself, is more than incidentally a means of combating hemolytic anemias, such as those due to the streptococcus or to the malaria parasite. The unrecorded experiments of Indians with Peruvian bark long antedate modern chemotherapy. The latest advance is that initiated by Domagk in 1933 by the discovery of the bacteriostatic action of a sulfonamide in experimental streptococcal infections. To discuss in detail the use of sulfonamides or quinine is obviously beyond the scope of these remarks. Chemotherapy may also be of value as an accessory in the treatment of blood dyscrasias of which an infection is an important complication. Thus, the advent of an infection of the respiratory or urinary tract may even be fatal in a patient with severe anemia otherwise easily amenable to therapy. The signs of infection, however, may be falsely simulated in a patient with a hemoglobin level of less than 25 per cent by a fever of 1 or 2°F. that may be entirely due to the anemia; even higher temperatures may result when an active hemolytic process is present entirely without infection. For the local tissue necrosis and secondary infection encountered, usually in the oral cavity, in agranulocytosis, aplastic anemia or leukemia, especially the monocytic variety, the relatively small experience available already indicates a value for the sulfonamides. Their utility consists in holding in check the invasion of the infection until other remedies may have an opportunity to act on the underlying blood dyscrasia.

It seems clear that in general, as in the presence of primary infections associated with leukopenia, the possibility of further depression of the granulocytes is not so great a risk as the danger from the infection when uncontrolled by chemotherapy. Sulfonamides, like certain other cyclic compounds, have caused acute hemolytic anemia, leukopenia, thrombopenic purpura and aplastic anemia. Fortunately, such undesirable results occur in only a very small percentage of cases, and their manifestations can usually be prevented by early detection. Because the chance of such an occurrence is small, one should never hesitate to administer these valuable drugs when a serious infection presents a clear indication for their use. On the other hand, the widespread and indiscriminate employment of the sulfonamides for trivial infections may well produce from only a small percentage incidence a

considerable number of hematologic complications, immediate or remote.

### SPLENECTOMY

In 1911, Micheli observed the benefit of splenectomy in a case of acquired hemolytic jaundice, and in the next two years, Eppinger and Banti independently reached the conclusion that it was a logical and successful procedure in congenital hemolytic jaundice. In this community, Dameshek has recently done a service by calling attention to various types of acquired hemolytic jaundice and by re-emphasizing the therapeutic value of splenectomy in some of them. The success of splenectomy in such anemias depends on the predominance of pathologic blood destruction in the spleen. In congenital hemolytic jaundice, the red blood cells almost invariably exhibit some increase in fragility in hypotonic saline solution, and the spleen is usually large and the pulp engorged with blood. A successful splenectomy is almost always dramatically effective in returning the patient's blood values to normal. If necessary, as a preliminary to operation, rapidly repeated transfusions should be given to bring the hemoglobin level to at least 50 per cent of normal. Although this may be difficult in the face of a crisis of rapid blood destruction, splenectomy not only promptly abolishes this phenomenon but also, by extrusion of blood from the spleen during operative manipulation, provides an autotransfusion, often immediately raising the hemoglobin level by 15 per cent or more. Consequently, splenectomy should not be unduly delayed.

In patients with acquired hemolytic jaundice, a term that includes several distinguishable acute and chronic forms of disease, a generalization concerning the effect of splenectomy is impossible. Perhaps, however, it can be stated that after certain causes of hemolytic anemia that are amenable to other forms of treatment have been excluded, splenectomy is likely to be beneficial if the fragility of the red blood cells in hypotonic saline solution is significantly increased and if the spleen is distinctly enlarged. Splenomegaly alone, however, provides no guarantee of success for splenectomy. Before the procedure is undertaken, the duration and nature of the hemolytic process should be carefully studied. Thus, in acute cases, the history may reveal exposure to hemolytic compounds, such as phenylhydrazine, sulfanilamide and arsine, or in other cases, dark urine (hemoglobinuria) after exposure to cold or after sleep. A blood culture or film may demonstrate septicemia due to bacteria or malaria parasites. Exposure to pure carbon dioxide causes anoxic microscopic sickling in sickle-cell anemia, and in paroxysmal nocturnal

hemolysis. A positive serologic test for syphilis and hemolysis on chilling (Donath-Landsteiner phenomenon) confirm the diagnosis of paroxysmal hemoglobinuria *e frigore*. Such patients are not suitable for splenectomy. In other patients, auto-agglutination of the red blood cells has been remarked; Dameshek has found hemolysins in the serum independent of isohemolysins in a certain group of cases. Bone-marrow biopsy or splenic puncture may disclose other causes of acquired hemolytic anemia, such as aleukemic leukemia, Hodgkin's disease and agnogenic myeloid metaplasia. Suffice it to say that if the conditions enumerated above, which are amenable to other types of therapy, can be excluded and if severe hemolytic anemia with acholuric jaundice and manifest signs of active blood regeneration persist for some days despite frequent transfusions, splenectomy may be indicated, at least as a means of somewhat reducing excessive blood destruction and, possibly, of abolishing it.

It is to be emphasized that the expectation of success from splenectomy in so-called "acquired hemolytic jaundice" is quite different from that in the congenital condition, and as in thrombopenic purpura, although splenectomy is the only therapy likely to be effective, its success is far from certain. Likewise, splenectomy in Banti's syndrome, in which the hypochromic anemia is probably to a considerable extent due to chronic and often occult bleeding from varices, is not always of benefit. The operation is often technically difficult because of the adherence of the spleen to nearby structures, and only when the obstructing vascular lesion is confined to the splenic vein is there considerable certainty of complete relief. Unfortunately, some type of hepatic cirrhosis is most frequently responsible for "chronic congestive splenomegaly," the highly appropriate descriptive term for Banti's syndrome that was coined several years ago by a Boston physician, the late Dr. Ralph C. Larrabee.

#### IRRADIATION

Irradiation by roentgen rays or radioactive phosphorus is today considered the chief weapon in treating leukemias and related conditions. Yet, although in discussions of such treatment great attention is paid to the number and character of the leukocytes, a disabling and frequently fatality-determining feature of leukemia is the anemia that sooner or later appears. Indeed, the problem in the irradiation of leukemias is not so much how to effect a reduction in the number of white blood cells as how to increase the number of red blood cells (or platelets). Since it is usually considered unsafe to apply x-ray therapy in the presence of severe anemia, preliminary transfusions to bring

the hemoglobin to a level of at least half the normal value are indicated.

The justification for discussing the use of irradiation, a highly technical procedure requiring special apparatus and experience, is that the best results from such therapy in leukemias can be obtained only when collaboration between clinician and roentgenologist is close and intelligent. It is assumed, for purposes of discussion, that the anemia in the leukemias is due to a considerable extent to the mechanical inhibition of normal red-cell production in the marrow cavity by overcrowding with immature leukocytes. In other cases of myelophthitic disease, the bone marrow is invaded by the cells of metastatic carcinoma or is replaced by lipoid-bearing cells or by fibrous or osseous tissue, as in osteosclerotic anemia. Because the cells of most metastatic carcinomas, like those of fibrous or osseous tissue, are presumably insensitive to irradiation, no improvement of the red-cell level is to be expected from irradiation in such cases. Accordingly, when there is doubt regarding the character of the disturbance in the marrow, sternal biopsy is indicated before one decides whether x-ray therapy is to be given.

Although the use of x-rays in the treatment of leukemia was introduced by Senn as early as 1903, it is even now difficult to choose the most suitable procedure and amount among the variety of methods and dosages that have been and still are employed. Experience agrees, however, that in acute leukemias the process is inherently of such a kind or its rate of progress is so rapid that irradiation is not only useless but detrimental. By contrast, in the management of chronic leukemias, especially the myelogenous, the skillful use of irradiation is frequently a means of providing a comfortable and useful existence during months or even years.

In the treatment of chronic leukemias, a trend can be observed toward the use of small amounts of irradiation applied to the body generally, in contrast to heavy local exposure of obviously enlarged organs, such as the liver and spleen. Because the abnormal cells in chronic leukemia diffusely invade the active bone marrow, this tendency seems logical. Since, however, it is never possible to gauge with accuracy the effect of a physical agent on a complex biologic system, overdosage of the entire bone marrow is most surely avoided by exposure of only a portion of it to the action of x-rays at one time. It is desirable, whenever possible, to avoid heavy local irradiation which, despite a selective effect on immature cells, injures all cells—even those of normal tissues. We have observed enlargement of the spleen to remain substantially undiminished after relative

doses of x-ray therapy applied locally, only to the organ later diminish in size, apparently a result of repeatedly administered small amounts of general irradiation. If an interval first of a few days and later a week or two allowed to elapse between exposures of a part of the body to no more than 75 to 100 r, leukocyte count preceding each contemplated irradiation becomes a good measure of the effects of previous therapy and thus tends to prevent overage. Finally, observation suggests that significant increase of red blood cells may not begin for several weeks after sufficient irradiation to cause marked lowering of the leukocyte count. Because seemingly within the somewhat narrow range dosage between suppression of leukocyte production in the marrow and suppression of erythropoiesis, that the effects of irradiation are most beneficial, it is desirable to proceed with sufficient deliberation to allow for observations on the production of both types of cells.

The use of radioactive phosphorus, logically introduced in the treatment of leukemias by Dr. H. Lawrence, of San Francisco, is still under evaluation. Nevertheless, it seems probable from the results already reported from several localities that radioactive phosphorus is not the final answer to the problem. The impression gained by one who, it should be said, has had no personal experience with the method is that it represents, like x-ray therapy, a form of irradiation theoretically more selective in its effects on leukemic cells and simple to administer. To my mind, however, it has the theoretical objection that all the hematopoietic organs are exposed simultaneously to irradiation. Nevertheless, eminently satisfactory results have been obtained with radioactive phosphorus in the treatment of chronic leukemias, especially those classified as myelogenous. It is still too early to be certain that such effects are superior to those obtained with modern x-ray treatment. In the management of acute leukemias, leukemic leukemias and leukemias in which severe anemia persists with or without previous x-ray treatment, radioactive phosphorus appears to be able to cause benefit as consistently as any other form of irradiation does.

#### TRANSFUSION

The final therapeutic aid in the treatment of anemia is blood transfusion. Today, the use of citrated blood, possessing as it does the important advantages of comparative leisure in collection and administration and convenience in transportation and storage, is the method of election. In spite of theoretical objections, fresh citrated blood apparently possesses no practical disadvantages compared with unaltered whole blood. Increased care in the

preparation of glassware, tubing and citrate solutions has eliminated many of the febrile reactions to such transfusions. Since, with anemia, the hemoglobin content of the recipient's blood is always reduced, whole blood rather than fresh, preserved or reconstituted plasma is the medium of choice. Thus, in the treatment of anemias, the plasma serves largely as a vehicle for the conveyance of red blood cells. Were it possible at present—when war places a premium on the collection of plasma—to discover a means of preserving the discarded red blood cells intact over relatively long periods, this by-product of emergency activity would no longer largely be wasted.

In the treatment of anemia, blood transfusion plays a significant, although entirely passive, role. Since the hemoglobin concentration in the circulating blood is increased, the blood is better able to carry oxygen from the lungs to the body tissues. With one unimportant exception, there is no evidence that transfusion has a stimulating action on the bone marrow, so far as the production of red or white cells or platelets is concerned. The exception is that, as a result of the eventual destruction of the transfused red blood cells, iron and possibly other materials necessary for new red-cell production may slowly be made available. This delayed and feeble action of transfusion, demonstrable only in hypochromic anemia, can scarcely compare with the effectiveness of the oral administration of a few grams of iron. On the other hand, there is no evidence that transfusion has any depressing effect on the bone marrow unless it raises the hemoglobin above normal values. Transfusion never passively raises the recipient's leukocyte count for more than a few minutes, but may, probably by introducing platelets, cause a cessation of bleeding in thrombopenic purpura for several hours or a few days. The effect of transfusion on bleeding in hemophilia is by virtue of the introduction of a clot-accelerating agent, probably enzymic, associated with the plasma globulins.

Transfusion provides a valuable and sometimes lifesaving procedure in the treatment of anemia, for it may give time for other methods of treatment to become effective or for spontaneous improvement to occur. Thus, patients with sufficiently low hemoglobin values may die before the effect of liver extract or iron therapy takes place. The use of transfusions as a means of carrying patients through hemolytic crises or of preparing them for splenectomy or for x-ray therapy has already been mentioned. In patients with a temporary suppression of red-cell production, as in benzol poisoning, adequate hemoglobin levels may be artificially maintained until Nature initiates new blood formation in the bone marrow. Finally, in aplastic anemia, or with aleukemic

leukemia, a reasonably comfortable existence may sometimes be prolonged for many months by the skillful use of transfusions alone.

For the effective employment of transfusions, two conditions must be met: blood must be readily available and of the proper type; and the technic of the transfusions must be satisfactory and their use judicious. The availability of suitable blood in urban communities is largely an economic question. In fact, the cost of repeated transfusions often becomes prohibitive for many persons able to employ private physicians. The relative difficulty of drawing blood in the past and the comparative rarity and dramatic setting of the procedure have much to do with the present high cost of a pint of blood in many localities. Rarely, today, does the professional donor from whom blood was formerly drawn by an incisional approach to his veins have this unnecessary cause to raise the value of his contribution. The solution, like that of other price situations depending on the economics of supply and demand, will probably come through extension of the organization and invention that have produced the blood bank, the volunteer-donor registry and the emergency blood-procurement service. It is logical to replace the iron lost by the donor by means of a two weeks' course of orally administered ferrous iron.

Time does not permit a discussion of the problems of blood typing except to say that mistakes can most certainly be avoided by the use of typing serums of high agglutinating titers. The relatively rare possibility of the development of anti-Rh agglutinins by the recipient during pregnancy or as a result of previous transfusions has recently been disclosed by the brilliant work of Landsteiner, Wiener, Levine and their associates. A final direct test involving incubation of the donor's cells in the recipient's serum for half an hour, with subsequent microscopic inspection, will almost certainly detect incompatibilities, although to determine their precise nature may require special methods. However, despite the use of compatible blood and of scrupulous care, some unknown quality of certain patients with anemia due to other causes than blood loss renders mild or even severe febrile reactions likely to occur.

From the recipient's point of view, the technic of transfusion includes skillful venipuncture with a short-bevel needle of small caliber that tends to minimize injury to the vein. The blood should be run in slowly, especially in severely anemic patients, to avoid a sudden increase in blood volume, which may overburden an already hard-pressed circulation. The alkalinization of the recipient's urine with 12 gm. of sodium bicarbonate, given an hour or two before transfusion, prevents the precipitation of hemoglobin in the renal tubules

if, for any reason, hemoglobinuria results from the transfusion. As a "biologic test," it is desirable to inject not more than 50 cc. of blood in the first half-hour and to watch for symptoms and signs of a reaction. In the management of patients with anemia, the fact that subsequent transfusions may be required should always be borne in mind. Although cutting down on the recipient's vein and its ligation after transfusion are rarely necessary, this unfortunate practice still exists. As a result, patients whose veins have been destroyed by several previous transfusions may present a serious technical problem. Fortunately, in such cases, it is sometimes possible to use the femoral vein or, according to the recent work of Tocantins, to infuse blood directly into the marrow cavity of the sternum. Aside from its physiologic benefit to the patient, the facile performance of transfusion has a desirable psychologic effect in dispelling the dramatic or ominous connotations of the method in the mind of the layman.

If the use of transfusions is to be fully effective, the objective to be obtained should be kept clearly in mind. For example, if the hemoglobin level of a patient with pernicious anemia is considered dangerously low for the interval of a few days before parenteral liver-extract therapy becomes effective, a single transfusion often suffices. On the other hand, in a patient with a type of anemia in which improvement may be long delayed or may never occur, transfusions repeated at appropriate intervals should be given to raise the hemoglobin and to maintain it at a level compatible with moderate activity in convalescence or at light work. It is a waste of precious and potentially useful weeks or months of such a patient's life if, owing to parsimony in the number of transfusions, he is needlessly confined to bed or home.

\* \* \*

It is a truism that proper treatment depends on accurate diagnosis of the type of anemia. Perhaps it is not so well known that this is often impossible from the examination of the blood alone but requires, as in any other field of medicine, careful history taking and physical examination and special laboratory examinations. The final proof of the correct diagnosis of nutritional-deficiency anemias is an orderly hematopoietic response to substitution therapy at the expected time. Because certain types of anemia may masquerade as cardiac, renal, nervous or even orthopedic conditions, a correct determination of the patient's hemoglobin level should be as routine a procedure as the performance of a urinary examination. Even when one is dealing with an incurable ailment, therapy effectively directed at an associated anemia may sometimes bring reward to both patient and physician.

## FAMILIAL NONHEMOLYTIC JAUNDICE\*

## Report of a Case with Liver Biopsy

JOHN J. CURRY, M.D.,† TIBOR J. GREENWALT, M.D.,‡ AND RUSSELL J. TAT, M.D.‡

BOSTON

UNDER the designation "familial nonhemolytic jaundice," Dameshek and Singer<sup>1</sup> recently reported a group of cases of mild acholuric jaundice occurring in several members of two families. Although congenital hemolytic jaundice as at first suspected in these cases because the in den Bergh reaction in the blood was "indirect" and the urine contained no bile, this diagnosis was conclusively ruled out because none of the evidences of increased blood destruction (spherulosis, increased hypotonic fragility, increased urobilinogen output and so forth) were present, and there was no evidence of increased activity on the part of the bone marrow (polychromophilia, reticulocytosis, high platelet count and so forth). On the other hand, organic hepatic disease seemed unlikely in view of the lack of progression of jaundice over a period of years and use of the various tests for liver function were negative. That the condition was due to a specific functional disturbance in the excretion of indirect bilirubin from the blood by hepatic cells was indicated by the bilirubin-excretion test, which invariably showed a marked retention of injected bilirubin. It was believed by these authors that the disease itself was organically normal, especially since L. J. and Lowenstein<sup>2</sup> had discovered families of affected rats with an identical picture in histologic studies of the livers were uniformly negative. Although Dameshek and Singer were unable to perform biopsies of the liver in their cases, Krarup and Roholm<sup>3</sup> recently reported of a similar or identical condition ("icterus juvenilis"<sup>4</sup>) in which aspiration biopsies of the liver were negative. In none of the cases<sup>5</sup> were biopsies of the liver reported. In present investigation, there was opportunity for a detailed study of a patient with the features of the familial nonhemolytic condition. A biopsy of the liver was performed at operation. In addition, it was possible to study sections of the spleen, which had been removed previously under the impression that the disease was one of familial hemolytic jaundice. The

results of these studies, which showed a normal histology of both the liver and spleen, are the subject of the present report. The lack of response to splenectomy again indicates the necessity for differentiating the disorder from hemolytic jaundice.

## CASE REPORT

P. M., a 50 year-old divorced Irishman, was admitted to the Third (Tufts) Medical Service of the Boston City Hospital on May 25, 1941 in a state of marked disorientation, possibly alcoholic.

Physical examination revealed a well developed and well nourished man with marked jaundice of the skin and scleras. There was no abdominal tenderness or spasm, the liver was not palpable, and there was a well healed longitudinal incision in the left upper quadrant. There were no abnormal neurologic signs, and the remainder of the physical examination revealed no significant abnormalities.

Under symptomatic treatment, the state of mental confusion cleared completely in 2 days, at which time the following history was elicited:

The patient and an older sister had been yellow since birth. The parents and three other siblings had never been jaundiced. A paternal cousin was jaundiced at birth, but the icterus soon disappeared. The patient had two children, neither of whom had ever been jaundiced, and there was no other history of jaundice in the family.

Because of their yellow color the patient and his sister shunned all social contacts, and were frequently ridiculed as "Chinks" by neighbors and even by members of their own family. This resulted in the formation of a close emotional attachment. As children, both developed normally. Neither had ever had pruritus or undue fatigue, nor had they noticed dark urine or clay-colored stools. They had never shown any gastrointestinal symptoms and the jaundice, although varying somewhat in intensity from time to time, had never been related to food intake. Since the age of 18, the patient had been a moderate whiskey drinker, bouts of drinking seemed to increase his jaundice.

The first admission, in May, 1918, was at another hospital, where the patient was admitted for study of his jaundice. The notation was then made that he had contracted syphilis 5 years previously, and had received oral mercurial therapy for 6 months. Positive physical findings at that time were icteric skin and scleras, splenomegaly (?) to 2 cm. below the left costal margin, and the presence of a penile scar. The blood Hinton reaction was positive. The laboratory data are presented in Table 1. The diagnoses were hereditary jaundice and syphilis. The patient was discharged to the Outpatient Department, but failed to attend.

He was next seen in August, 1923, at the Boston City Hospital, this time because of "nervousness." Physical examination, except for jaundice, was entirely negative. The laboratory data are shown in Table 1. A diagnosis of hereditary jaundice was also made.

\*Third (Tufts) Medical Service, Boston City Hospital and the Henry Boston Dispensary.  
†Was aided by a grant from the Chilton Fund, Tufts College.

‡Present Third (Tufts) Medical Service, Boston City Hospital, fellow in hematology, Boston Dispensary and Joseph H. Pratt Hospital.

The patient was readmitted in September, bleeding profusely from self-inflicted slashes of the wrists and neck. He revealed that he had "double-crossed" his jaundiced sister in a real estate transaction and, in a state of marked depression, had attempted suicide. Physical examination revealed lacerations of the neck from ear to ear, and several smaller lacerations of both wrists. Except for jaundice, no physical abnormalities were noted. On entry, the patient presented a picture of marked hypochromic anemia due to blood loss. Extensive laboratory studies were performed (Table 1). A diagnosis of atypical familial acholuric jaundice was made, and splenectomy was recommended.

On November 19, when the blood had returned to normal, splenectomy was performed. At operation, the spleen

Liver-function tests showed no bromsulfalein retention after 15 minutes. Another determination showed 20 per cent retention in 15 minutes. The hippuric acid excretion was 3 gm. Bilirubin-excretion tests were performed on three occasions, but the results, although indicating marked retention, proved unsatisfactory, owing to the unusually high fasting-serum-bilirubin level. The prothrombin time was normal. The daily fecal urobilinogen output ranged from 8 to 25 mg. (normal 50 to 200 mg. per day). This was unaltered by the daily administration of 1.2 gm. of sodium dehydrocholate (Decholin) intravenously.

On x-ray examination, the patient's chest and skull showed no abnormality. The gall bladder failed to visualize after oral cholecystography. Intravenous cholecysto-

TABLE 1. *Summary of Significant Laboratory Data.*

DATE	RED-CELL COUNT  × 10 <sup>6</sup>	HEMO- GLOBIN  %	WHITE-CELL COUNT  × 10 <sup>3</sup>	HEMATO- CRIT  %	RETICULO- CYTES  %	RED-CELL FRAGILITY  % NaCl	SERUM BILIRUBIN  mg./100 cc.	VAN DEN BERGH REACTION	SEROLOGIC TEST FOR SYPHILIS
1918	7.44 6.96	80 127	8.4 11.6						++
1923									
Before splenectomy	2.65 3.38 2.70 4.25 5.10	50 55 50 63 90	4.60 6.20		2.0 1.6 2.0	0.46-0.32 0.40-0.28	10.0 6.7 9.0 10.0	Delayed direct	0
After splenectomy	4.78 5.42	72 90	14.50 8.00	48.0	0.2		2.3	Delayed direct	0
1941	4.55 4.80 4.11 5.02 5.02	98 95 91 96 90	16.15 9.04 11.50 13.90	45.5 42.0 47.0 47.0	0.0 0.0 1.0 1.2 1.2		3.4 6.6 9.2 4.5 10.4 12.6	Indirect	+++

was found to be normal in size and consistence. The jaundice became somewhat less intense following operation.

During convalescence, the patient developed auditory hallucinations and was committed to the Boston State Hospital, where he remained for 14 years as a case of manic-depressive psychosis, depressed state, and where his stay was uneventful.

After discharge, he was employed as a restaurant worker, and enjoyed good health until admission to the Boston City Hospital.

Examination of the blood showed a red-cell count of 5,020,000 with a hemoglobin of 14 gm. (90 per cent), and a white-cell count of 13,900 with 1,900,000 platelets and 1.2 per cent reticulocytes. The hematocrit was 47 per cent, the mean corpuscular volume was 94 cu. microns, the mean cell diameter was 8 and the mean cell thickness was 1.87 microns. The blood smear showed 54 per cent polymorphonuclears, 34 per cent lymphocytes, 3 per cent monocytes, 7 per cent eosinophils and 2 per cent basophils, with occasional target cells and Howell-Jolly bodies. Rouleaux formation was normal. The red-cell fragility to hypotonic saline solutions began at 0.44 and was complete at 0.12 per cent. An aspiration biopsy of the sternal marrow was negative.

Numerous urinalyses revealed no bile or increase in urobilinogen content. The serum bilirubin ranged from 3.4 to 12.6 mg. per 100 cc. in fasting blood samples, and always gave the indirect van den Bergh reaction. The total serum protein was 5.6 gm. per 100 cc., with 3.8 gm. albumin and 1.8 gm. globulin. The blood cholesterol was 240 mg. per 100 cc., with esters accounting for 180 mg. The bile acids (Thannhauser and Ginsburg<sup>6</sup>) were 2 mg. per 100 cc. The blood Hinton reaction was positive.

grams revealed a normally functioning gall bladder. A gastrointestinal series showed a chronic duodenal ulcer, and a barium enema revealed a diverticulum of the sigmoid.

Exploratory laparotomy was performed on August 26, under spinal anesthesia. At operation, the liver was normal in size and consistence. The gall bladder was normal in size, color and thickness of wall, and emptied easily on normal pressure. There were many adhesions between the omentum and the site of splenectomy. A small piece of liver tissue was removed.

Histologic examination of sections of the liver was reported as follows:

The architecture is well preserved. There is a clearly recognizable capsule, and the portal areas, central veins and lobules stand out distinctly. About one third of the portal areas have a slight increase in fibrous tissue and show a moderate lymphocytic infiltration. The smaller branches of the portal vein, the hepatic artery and the smaller tributaries of the biliary system show no evidence of disease. There is no bile stasis, and no dilatation of the bile ducts or bile canaliculi.

The liver cells are well preserved, vary in glycogen content, and contain no recognizable fat. The cytoplasm is granular. There are no giant or necrotic cells. There are no mitoses, and no cells contain alcoholic hyalin.

Pigment is present in the liver cells. There is a very little powdery brownish-green pigment in the liver cells adjacent to the central veins; this does not stain for iron. There is a little iron-containing pigment concentrated about the bile canaliculi in isolated nests of liver cells. There is a third pigment, which is also brown to greenish brown in many liver cells; this is not iron

staining (it is not like the pigment of bile stasis). There is no demonstrable hemofuscin.

The endothelial cells are present, free of pigment and inconspicuous.

There is no edema, and no thrombosis or hemorrhage.

The sections of the spleen removed in 1923 were also viewed. The result of microscopic study was: "The spleen shows reticulum-cell and endothelial cell hyperplasia, leukocytosis, eosinophilia and moderate hemosiderosis."

Laboratory studies performed on the patient's sister showed a red-cell count of 3,940,000 with 76 per cent hemoglobin, and a white-cell count of 7250, the serum proteins were 7.5 gm. per 100 cc., the albumin being 5.2 g. and the globulin 2.3 gm. The red cell fragility to isotonic saline solution began at 0.40 and was complete at 0.32 per cent. The serum bilirubin was 11.9 mg. per 100 cc., and the van den Bergh reaction was indirect. The blood Hinton reaction was negative.

### DISCUSSION

All the characteristic features of familial non-hemolytic jaundice were present in this patient.

The familial nature of the disease was established by study of the patient's fifty-four year-old sister, who had been jaundiced since birth. She was in perfect health, had no complaints and gave no history of alcoholism. Although she was markedly icteric, there was neither hepatomegaly nor splenomegaly. Laboratory data revealed no anemia and a hyperbilirubinemia of the indirect variety. The blood Hinton reaction was negative.

The nonhemolytic nature of the jaundice was revealed by the absence of anemia, reticulocytosis and bone-marrow hyperplasia, the low fecal urobilinogen and the normal urinary urobilinogen values and, finally, the failure of the patient's condition to respond to splenectomy. In addition, the spleen was grossly and microscopically normal.

The absence of organic liver disease was confirmed by the findings at laparotomy. The liver was grossly normal, and the biliary system intact; microscopic examination of a liver biopsy specimen was within normal limits. Alcoholic and syphilitic liver disease were thus ruled out. Numerous tests of liver function—hippuric acid synthesis, bromsulphalein excretion, cholesterol partition and prothrombin concentration—were within normal limits. Bilirubin-excretion tests, although difficult to interpret because of the high fasting levels of bilirubin in the blood, showed a definite tendency toward abnormal retention. It is significant that although a high level of indirect bilirubin was present in the blood, there was a low output of urobilinogen in the feces; this indicated, without further testing, bilirubin retention.

This case is of further interest because it afforded the opportunity of studying the hematologic changes eighteen years after splenectomy. These

changes have recently been emphasized by Singer, Miller and Dameshek<sup>7</sup> and are well brought out in the case presented. Thus, there was leukocytosis, with lymphocytosis, occasional target cells and Howell-Jolly bodies, increased platelets, increased hypotonic resistance of the red cells and decreased output of urobilinogen in the feces. The excessively low values for fecal urobilinogen were probably due to the summation of the two factors of delayed bilirubin excretion and splenectomy.

In an attempt to increase the bilirubin excretion, sodium dehydrocholate (Decholin) was injected intravenously on two occasions. In the first experiment, 0.6 gm. was injected twice daily for four days, and the stools were collected during this period. In the second, 4.0 gm. was injected in one dose, and stools were collected for the subsequent four days. On neither occasion was there any increase in the fecal urobilinogen. A control patient with normal urobilinogen excretion also failed to show an increase after one injection of 4 gm. of sodium dehydrocholate intravenously.

This patient represents a living example of the necessity for differentiating familial nonhemolytic and familial hemolytic jaundice. Dameshek and Singer<sup>1</sup> have presented detailed data for making this differentiation possible and have stressed the fact that acholuric jaundice and an indirect van den Bergh reaction need not indicate a hemolytic process. In this and other studies, the value of the fecal urobilinogen output for determining the presence or absence, as well as the degree, of increased hemolysis has become increasingly apparent. Splenectomy in the case presented above apparently reduced the degree of bilirubinemia temporarily, probably through its effect on blood destruction. The contrast between the dramatic cessation of jaundice in familial hemolytic jaundice and the results in this case is indeed striking.

The possibility of familial nonhemolytic jaundice should be considered in every case of persistent, relatively mild, nonobstructive jaundice. It is believed that the condition is commoner than the small number of reported cases indicate.

### SUMMARY

A case of familial nonhemolytic jaundice, with biopsy of the liver, is presented. Splenectomy performed eighteen years previously for "familial hemolytic jaundice" failed to alter the course of the disease. The hematologic effects of splenectomy were apparent.

The injection of large doses of sodium dehydrocholate failed to increase the fecal urobilinogen excretion.



The importance of differentiating the familial nonhemolytic condition from congenital hemolytic jaundice is emphasized.

Since this paper was written we have studied four additional cases of familial nonhemolytic jaundice, occurring in three families.

#### REFERENCES

- 1 Dameshek, W., and Singer, K. Familial nonhemolytic jaundice: constitutional hepatic dysfunction with indirect van den Bergh reaction. *Arch. Int. Med.* 67:259-285, 1941.

- 2 Malloy, H. T., and Lowenstein, L. Hereditary jaundice in the rat. *Canad. M. A. J.* 42:122-125, 1940.
- 3 Krarup, N. B., and Roholm, K. Histologic studies by means of liver biopsy in intermittent jaundice of young persons. *Ugesk. f. læger.* 103:72-75, 1941.
- 4 Meulengracht, E. Icterus intermittens juvenilis (chronischer intermittierender juveniler Subikterus). *Klin. Wchnschr.* 18:118-121, 1939.
- 5 Rozendaal, H. M., Comfort, M. W., and Snell, A. M. Slight and latent jaundice. *J. A. M. A.* 104:374-381, 1935.
- 6 Thannhauser, S. J., and Ginsburg, E. Unpublished data.
- 7 Singer, K., Miller, E. B., and Dameshek, W. Hematologic changes following splenectomy in man, with particular reference to target cells, hemolytic index and lysolecithin. *Am. J. M. Sc.* 202:171-187, 1941.

### PILI TORTI HEREDITARIA\*

BERNARD APPEL, M.D.,† AND SALVATORE J. MESSINA, M.D.‡

BOSTON

THE name "pili torti" was first applied by Ronchese<sup>1</sup> in 1932 to a rare developmental anomaly of the hair. He reported the case of a seven-year-old girl, born in Rhode Island, of Italian descent, who was the youngest of eight children and was apparently normal in every other respect except that the teeth were poor and slightly notched, with spaces between them; the hairs on the scalp were dull blond, lank and frizzly, with a wild bushy appearance. The hair had never been cut but broke spontaneously on slight injury at various short lengths from the scalp. Ronchese made numerous interesting and fairly thorough studies of the hair roots and of the hair shaft in various mediums, measured the elasticity and strength of the hair, and examined the hair follicles microscopically. He also discussed the meager previous literature on the subject and came to the conclusion that his case was the second reported in the literature, in which the hair was characterized by fragility and sharp twists on its own axis. He proposed the name of "twisted hairs." His report has been quoted elsewhere in the literature.<sup>2</sup>

Ronchese presented the same case at the Atlantic Dermatological Conference, March 22, 1941, in Boston. During the interval, the patient had been treated only with fairly constant applications of lanolin. Her hair had grown out fairly long, and there was a marked improvement in the general appearance. She was able at that time to dress her hair so that it attracted no attention and appeared quite normal to the casual observer. At a subsequent date, the sister, two years younger than the patient, was examined and showed a similar but much milder condition. There were

no definite areas of alopecia of the scalp, but the hair showed the same tendency to twisting, and there was a moderate degree of alopecia of the outer two thirds of the eyebrows. This patient did not show any dental hypoplasia.

Although recognizing that Ronchese first called attention to this condition in 1932, Sutton and Sutton<sup>2</sup> call the disease "pili torti (Galewsky)." It may be presumed that Galewsky's name was added because he<sup>3</sup> described a knotted condition, which he called "trichonodosis," in 1906.

In 1924, Ormsby and Mitchell<sup>4</sup> presented a case of so-called "atrophia pilorum monilethrix" in a two-year-old girl who was born without hair and whose scalp remained smooth until the age of fourteen months. Subsequently, the hairs resembled the beaded hairs in monilethrix, but on careful examination this appearance was thought to have been due to a twisting rather than to a beading of the individual hairs. In discussing the case, Foerster<sup>5</sup> stated that the condition resembled monilethrix, but that under the microscope the hairs showed twisting without any break. The same case was presented under the title "atrophia pilorum" by Ormsby and Mitchell<sup>6</sup> in 1925. At that time, there had been a marked improvement in the general appearance, the hairs had grown longer, and the former beaded appearance was less apparent; Dr. Ormsby, in the discussion, stated that he had not been able to prove that there was either twisting or actual beading of the hairs but that there was unquestionably a congenital atrophy.

Danforth,<sup>7</sup> in his studies on hair, mentions the twisting of hairs on their own axes. He apparently considers this a fairly normal phenomenon, varying in its degree in different hairs. The twisting causes a series of half turns so that one side of the hair is alternately toward and away from the observer. The length of the hair involved in the twist ranges from one to several millimeters. The greater distance renders the detection of the twist-

\*From the Department of Dermatology, Tufts College Medical School, and the Department for Diseases of the Skin, Boston City Hospital.

†Assistant professor of dermatology, Tufts College Medical School; assistant visiting physician, Department for Diseases of the Skin, Boston City Hospital.

‡Assistant in the Department for Diseases of the Skin, Boston City Hospital.

ing more difficult. When the twists are closely connected, the hair is given a frizzly character. This twisting, which is apparently irreversible and may even be seen within the follicle, is probably determined by the follicle, perhaps by periodic changes in the functions of the papilla. Danforth is of the opinion that this twisting may have an anthropologic significance. Franchi<sup>8</sup> believes that the condition may be due to endocrine damage acting on the sympathetic nervous system.

Hellier et al.<sup>9</sup> described the first case reported from England. They also apparently erroneously credited this name to Galewsky, but Ronchese<sup>10</sup>

since the authors found that the twisted hairs, when wet, stretched just as far as normal hairs, they conclude that if these hairs were kept damp there would be less risk of premature breaking.

Within the last few years, several other cases have been reported of which Sutton and Sutton<sup>2</sup> present a complete bibliography.

#### CASE REPORT\*

C. F., a 10-year-old girl, was first seen in the Out-Patient Department for Diseases of the Skin at the Boston City Hospital because of an eruption on the face. This was diagnosed as dermatitis venenata, probably

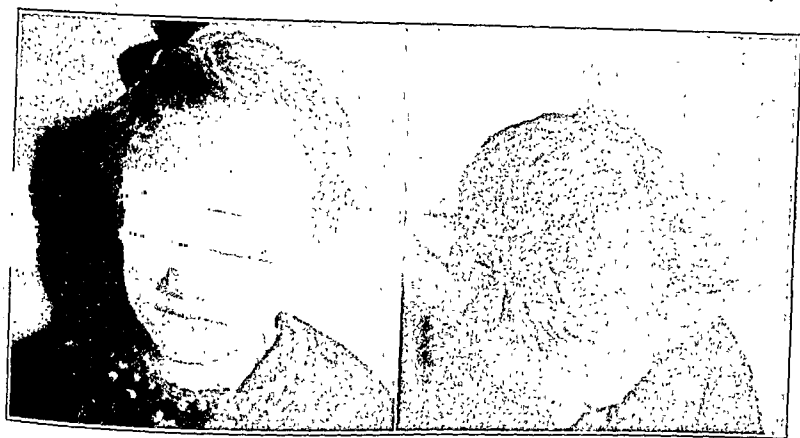


FIGURE 1. Patient's Younger Sister.

*Note that the pili torti hereditaria is relatively slight.*

led attention to his priority in this nomenclature. Hillier and his associates described a two-year-old girl with a fairly typical case, which apparently was at first provisionally diagnosed as alopecia. An interesting observation that they made points more definitely to a predetermined type, characteristically residing in the follicle, as the underlying feature producing the twist in the hair. They epilated with thallium acetate by electrolysis, following which follicular hyperkeratosis was observed; a few months later, when new hair grew in, it still had the characteristic twists. They made x-ray and optical examinations of these hairs and came to the conclusion that the irregularities were not due to any molecular disturbance of the hair recognizable by x-ray diffraction. The tensile strength of hair in their case showed that the normal hairs were about 10 per cent weaker when dry and 25 per cent weaker when wet, which was too far removed from normal. Moreover,

caused by a patent mange cure, which had been applied to the scalp by the mother. With usual soothing remedies and the cessation of the use of the preparation, the dermatitis promptly improved.

The mother stated that the patient had had a peculiar twisting type of hair since birth. It was somewhat worse when she was younger. Bald areas over the scalp and over the eyebrows were present constantly and were very disturbing. For the preceding 2 months, a large area of relative alopecia over the vertex of the scalp had developed. An older brother and a younger sister of the patient had a similar but definitely less noticeable type of hair; only on careful inspection did the twisting become obvious. The hair of these siblings was softer and could be dressed in a less conspicuous manner, but there was the same tendency toward the thin, straight, frizzled appearance, particularly in the shorter hairs (Fig. 1). The eyebrows were quite thinned out in their outer portions. The younger sister showed no changes in the enamel of her teeth. Her general physical condition was normal. The paternal

\*This case was presented at the Atlantic Dermatological Conference, Boston, March 22, 1941.

The importance of differentiating the familial nonhemolytic condition from congenital hemolytic jaundice is emphasized.

Since this paper was written we have studied four additional cases of familial nonhemolytic jaundice, occurring in three families.

#### REFERENCES

1. Dameshek, W., and Singer, K. Familial nonhemolytic jaundice: constitutional hepatic dysfunction with indirect van den Bergh reaction. *Arch. Int. Med.* 67:259-285, 1941.

2. Malloy, H. T., and Lowenstein, L. Hereditary jaundice in the rat. *Canad. M. A. J.* 42:122-125, 1940.
3. Krarup, N. B., and Roholm, K. Histologic studies by means of liver biopsy in intermittent jaundice of young persons. *Ugesk. f. Læger.* 103:72-75, 1941.
4. Meulengracht, E. Icterus intermittens juvenilis (chronischer intermittierender juveniler Subikterus). *Klin. Wchnschr.* 18:118-121, 1939.
5. Rozendaal, H. M., Comfort, M. W., and Snell, A. M. Slight and latent jaundice. *J. A. M. A.* 104:374-381, 1935.
6. Thannhauser, S. J., and Ginsburg, E. Unpublished data.
7. Singer, K., Miller, E. B., and Dameshek, W. Hematologic changes following splenectomy in man, with particular reference to target cells, hemolytic index and lysolecithin. *Am. J. M. Sc.* 202:171-187, 1941.

### PILI TORTI HEREDITARIA\*

BERNARD APPEL, M.D.,† AND SALVATORE J. MESSINA, M.D.‡

BOSTON

THE name "pili torti" was first applied by Ronchese<sup>1</sup> in 1932 to a rare developmental anomaly of the hair. He reported the case of a seven-year-old girl, born in Rhode Island, of Italian descent, who was the youngest of eight children and was apparently normal in every other respect except that the teeth were poor and slightly notched, with spaces between them; the hairs on the scalp were dull blond, lank and frizzly, with a wild bushy appearance. The hair had never been cut but broke spontaneously on slight injury at various short lengths from the scalp. Ronchese made numerous interesting and fairly thorough studies of the hair roots and of the hair shaft in various mediums, measured the elasticity and strength of the hair, and examined the hair follicles microscopically. He also discussed the meager previous literature on the subject and came to the conclusion that his case was the second reported in the literature, in which the hair was characterized by fragility and sharp twists on its own axis. He proposed the name of "twisted hairs." His report has been quoted elsewhere in the literature.<sup>2</sup>

Ronchese presented the same case at the Atlantic Dermatological Conference, March 22, 1941, in Boston. During the interval, the patient had been treated only with fairly constant applications of lanolin. Her hair had grown out fairly long, and there was a marked improvement in the general appearance. She was able at that time to dress her hair so that it attracted no attention and appeared quite normal to the casual observer. At a subsequent date, the sister, two years younger than the patient, was examined and showed a similar but much milder condition. There were

no definite areas of alopecia of the scalp, but the hair showed the same tendency to twisting, and there was a moderate degree of alopecia of the outer two thirds of the eyebrows. This patient did not show any dental hypoplasia.

Although recognizing that Ronchese first called attention to this condition in 1932, Sutton and Sutton<sup>2</sup> call the disease "pili torti (Galewsky)." It may be presumed that Galewsky's name was added because he<sup>3</sup> described a knotted condition, which he called "trichonodosis," in 1906.

In 1924, Ormsby and Mitchell<sup>4</sup> presented a case of so-called "atrophia pilorum monilethrix" in a two-year-old girl who was born without hair and whose scalp remained smooth until the age of fourteen months. Subsequently, the hairs resembled the beaded hairs in monilethrix, but on careful examination this appearance was thought to have been due to a twisting rather than to a beading of the individual hairs. In discussing the case, Foerster<sup>5</sup> stated that the condition resembled monilethrix, but that under the microscope the hairs showed twisting without any break. The same case was presented under the title "atrophia pilorum" by Ormsby and Mitchell<sup>6</sup> in 1925. At that time, there had been a marked improvement in the general appearance, the hairs had grown longer, and the former beaded appearance was less apparent; Dr. Ormsby, in the discussion, stated that he had not been able to prove that there was either twisting or actual beading of the hairs but that there was unquestionably a congenital atrophy.

Danforth,<sup>7</sup> in his studies on hair, mentions the twisting of hairs on their own axes. He apparently considers this a fairly normal phenomenon, varying in its degree in different hairs. The twisting causes a series of half turns so that one side of the hair is alternately toward and away from the observer. The length of the hair involved in the twist ranges from one to several millimeters. The greater distance renders the detection of the twist-

\*From the Department of Dermatology, Tufts College Medical School, and the Department for Diseases of the Skin, Boston City Hospital.

†Assistant professor of dermatology, Tufts College Medical School; assistant visiting physician, Department for Diseases of the Skin, Boston City Hospital.

‡Assistant in the Department for Diseases of the Skin, Boston City Hospital.

From the observations on one of Ronchese's patients, it is also reasonable to assume that, as the patients become older, there is a natural tendency for the hair to become less abnormal in appear-

## REFERENCES

- 1 Ronchese F Twisted hairs (pili torti) *Arch Dermat & Syph* 26 98 102 1932
- 2 Sutton R L and Sutton R L, Jr *Diseases of the Skin Tenth edition* 1549 pp St Louis C V Mosby Co 1939 P 1391
- 3 Galewsky Über eine noch nicht beschriebene Haaserkrankung (Trichon odosis) *Arch f Dermat u Syph* 81 195 1906

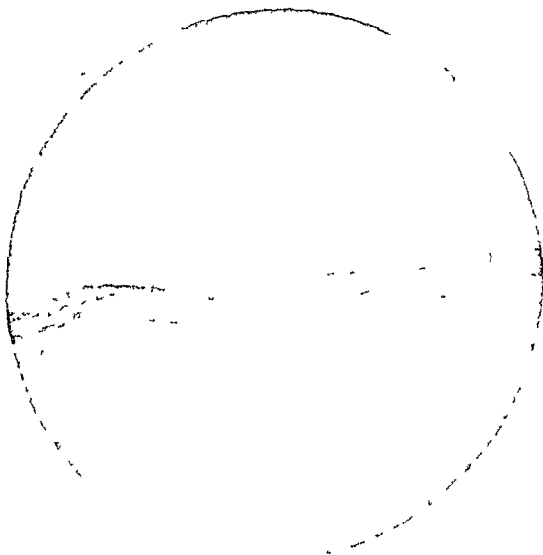


FIGURE 3 Microscopic Evidence of Twisting and Loosening of Keratin in Strandlike formation (hair mounted in canada balsam)

ance. The application of lanolin is apparently the only effective treatment known at present

## SUMMARY

A case of pili torti hereditaria is presented, and other cases reported in the literature are discussed, particularly from the point of view of etiology, which may well be an ectodermal hypoplasia

- 4 Ormsby and Mitchell Atrophia pilorum monilethrix *Arch Dermat & Syph* 10:393 1924
- 5 Foerster Discussion of Ormsby and Mitchell *Arch Dermat & Syph* 12 146 1925
- 6 Ormsby and Mitchell Atrophia pilorum *Arch Dermat & Syph* 12 76 94, 1925
- 7 Danforth C H Studies on hair *Arch Dermat & Syph* 12 76 94, 1925
- 8 Franchi F Su una duplice anomalia congenita ed ereditaria del sistema pilifero pili torti e fragili (spirotrichorexi) ed aplasia monile forme (monilethrix) *Arch ital di dermat* 10 267 301 1934
- 9 Heller F F Astbury W T and Bell F G A case of pili torti: clinical description, x-ray and optical examination *Brit J Dermat & Syph* 52 1 3 182 1940
- 10 Ronchese F Letter to the editor *Brit J Dermat & Syph* 53:25, 1941

## TYPHUS FEVER IN MASSACHUSETTS\*

### Report of a Case Contracted in an Out-of-State Endemic Area

JUSTIN E. HAYES, M.D.,† AND CHARLES E. GILL, M.D.‡

NORTHAMPTON AND WESTFIELD, MASSACHUSETTS

THE comparative rarity of the rickettsial diseases, typhus fever and Rocky Mountain spotted fever, in Massachusetts prompted the report of the following case. Although typhus fever is endemic to the extent of about 3000 cases each year throughout the United States, much of the illness is confined to the South Atlantic and Gulf states.<sup>1,2</sup> Very few cases have been reported from the New England states, and only 16 cases have been reported in Massachusetts since 1929,<sup>3</sup> including a series of 10 cases observed at the Beth Israel Hospital in Boston between 1929 and 1932 and reported in 1933.<sup>4</sup> Rocky Mountain spotted fever was first reported in the states east of the Mississippi River as early as 1931, and its prevalence since that time has been confined largely to the South Atlantic states.<sup>5</sup> The cases in the United States have numbered almost 500 annually in recent years. Three cases have been reported in Massachusetts since 1938, and 2 additional cases were reported in Rhode Island in 1937.<sup>3,6</sup>

#### CASE REPORT

A 55-year-old woman was admitted to the Cooley Dickinson Hospital on March 17, 1941, with the principal complaint of fever, first noted on March 12; the temperature was 103 and 104°F., respectively, on March 15 and 16. This patient, a teacher by occupation, had been known to one of us (J. E. H.) for some years, and the past medical history was entirely negative, except for a cholecystectomy in 1938.

Physical examination on admission revealed very little except the presence of fever and an eruption over the abdomen resembling rose spots. On the 2nd hospital day, this lesion covered the chest, neck and face, and a slight hacking cough appeared. Further extension of the rash was noted on the 3rd and 4th hospital days, with spread to the upper and lower extremities. The eruption was maculopapular and confluent in places, very itchy and dullish red, and at first bore some resemblance to measles. Distinct involvement of the palms and soles was noted. The rash persisted for the next 4 days and slowly disappeared by fading and scaling, complete disappearance being noted on the 10th hospital day. Physical examination of the chest revealed a few rales over the left base, and x-ray evidence pointed to congestion in the same area. The temperature from the time of admission ranged between 102 and 104°F. until slow lysis appeared on the 8th hospital day, or 13 days after the onset of fever. The patient was discharged from the hospital on the 14th day after admission, and recent inquiry indicates complete recovery. Supportive treatment was given as indicated.

\*From the Cooley Dickinson Hospital and the Massachusetts Department of Public Health.

†Physician-in-chief, Cooley Dickinson Hospital, Northampton, Massachusetts.

‡State district health officer, Westfield State Sanatorium, Westfield, Massachusetts.

Urinalyses on two occasions revealed a trace of albumin. Repeated examinations of the blood showed a slight reduction in the red-cell count during the course of the illness. The white-cell count fluctuated between 4700 on admission and 8700 on discharge. Polymorphonuclears ranged from 51 to 80 per cent, the lymphocytes ranging from 16 to 48 per cent; the relative lymphocytosis was most marked on admission. The blood Hinton reaction was negative. Blood cultures on the 2nd and 6th hospital days were negative. Stool culture on the 3rd hospital day revealed no organisms of the typhoid-paratyphoid group. Agglutination tests for typhoid, paratyphoid and undulant fever and the Weil-Felix reaction were negative on the 2nd hospital day. These tests were repeated on the 4th hospital day, and the Weil-Felix reaction was positive in a dilution of 1:40. The titer of the reaction increased to 1:400 on the 10th hospital day and fell to 1:80 in September. Isolation of the suspected infectious agent by guinea-pig inoculation of the blood was not done.

The assistance of the National Institute of Health, United States Public Health Service, was secured in the differential diagnosis of typhus and Rocky Mountain spotted fever. A blood specimen obtained on the 11th hospital day was reported positive to the Weil-Felix reaction in a dilution of 1:5120. The complement-fixation test for typhus recently developed in that laboratory was applied and gave a positive test in a dilution of 1:128. Additional specimens were submitted the following September and October, and the most recent titer of the Weil-Felix reaction was noted to be 1:80, the complement-fixation test being positive in all dilutions up to and including 1:512.

Further inquiry concerning the recent travels of this patient revealed that she had left Northampton on February 16, in the company of a fellow teacher, for an automobile trip to Florida. They arrived in Florida on February 26, and the patient resided until March 13 at the home of a cousin. Mild weather enabled her to indulge in considerable outdoor activity, including swimming and picnicking. No particular exposure to ticks, fleas or lice was noted. However, a prominent scabbed area resembling an insect bite was noted in the left scapular region at the time of hospital admission, and this was considered an extraordinary finding by the patient and her companion. The end of their visit in Florida came the day after the appearance of the fever on March 12. This did not prevent the patient's return, although she was obliged to seek medical assistance in Washington on March 15 and 16, when examination revealed a few "spots" on the abdomen and a temperature of 104°F. The remainder of the trip was made by train.

Much diagnostic confusion was created by the unusual clinical features of this case, and typhoid fever was the first illness suspected. The first four days in the hospital brought the development of the rash to a point where a virus or rickettsial illness was considered. The sustained fever, along with the unusual distribution of the eruption over the palms, soles and head, caused the

attending physician (J.E.H.) to suspect Rocky Mountain spotted fever. Subsequent laboratory work confirmed the presence of a rickettsial infection and made the earlier diagnosis of typhoid fever unlikely. Closer study of the epidemiologic features of the rickettsial infections indicated that typhus fever was the more probable diagnosis. The relative rarity of Rocky Mountain spotted fever in the early months of the year and the year-round incidence of typhus fever reinforced this impression. Furthermore, this patient had recently returned from an area of relatively high incidence of typhus fever.

Correspondence with the United States Public Health Service brought further support for the diagnosis of typhus fever. Their assistance was secured in the testing of the serum of this patient by means of the complement-fixation reaction recently developed by Bengston and Topping,<sup>7</sup> of the National Institute of Health. Tests on two occasions were clearly positive. Recent studies from the same source indicate a high degree of specificity for this test.

Since no specific serotherapy was available, only supportive and symptomatic treatment was given this patient. The sulfonamide drugs were not used.

## SUMMARY

The details of a recent case of typhus fever in a Massachusetts resident are presented. It is likely that the infection was contracted in an out-of-state endemic area recently visited by the patient.

In the differential diagnosis, a specific complement-fixation test recently developed at the National Institute of Health was utilized. Isolation of the infectious agent by animal inoculation was not attempted.

The recent prevalence of two common rickettsial illnesses, Rocky Mountain spotted fever and typhus, in the United States and in Massachusetts is briefly reviewed.

## REFERENCES

- 1 *Typhus Fever*. United States Public Health Service Leaflet R 927 3 pp. Washington: Government Printing Office, 1939.
- 2 *Annual Report of the Surgeon General, United States Public Health Service, 1940* 191 pp. Washington: Government Printing Office, 1941.
- 3 *Annual Reports of Massachusetts Department of Public Health, 1941* 1940.
- 4 Frustene, A. C., and Riseman, J. E. F. Endemic typhus fever in Boston: a report of ten cases. *New Eng. J. Med.* 209:542-545, 1933.
- 5 Hampton, H. C., and Fubank, H. G. Rocky Mountain spotted fever. *Pub. Health Rep.* 53:984-990, 1938.
- 6 Pihler, L. S. Rocky Mountain spotted fever in Massachusetts: report of a case. *New Eng. J. Med.* 219:378-382, 1938.
- 7 Bengston, I. A., and Topping, N. H. Specificity of complement fixation test in endemic typhus fever, using rickettsial antigen. *Pub. Health Rep.* 56:1723-1727, 1941.

## MEDICAL PROGRESS

### VASCULAR DISORDERS OF THE EXTREMITIES

JOHN HOMANS, M.D.\*

BOSTON

#### OBSTRUCTIVE ARTERIAL DISEASE OF LEGS

##### *Clinical Tests for Peripheral Arterial Deficiency*

THE usefulness of the simpler tests in confirming or refuting the results of the history and routine physical examination is discussed by Montgomery, Naide and Freeman.<sup>1</sup> In all vascular deficiencies, an estimate of the reduction of the arterial supply and the amount of the collateral circulation should be made. A rough estimate of arterial blood flow is secured by observation of the color of the toes when the legs are elevated to an angle of 30° for a minute or two (rapid paling is unfavorable; persistence of pinkness is favorable) and when they are depressed (delay in appearance of pinkness followed by rubor is unfavorable;

rapid appearance and persistence of pinkness is favorable).

In connection with the degree of arterial deficiency, the level at which the arteries are seriously constricted or occluded can be discovered by *oscillometry* and by the *histamine test*. After the state of the peripheral pulses in the feet and legs has been learned, the vigor of the pulse wave at various levels should be observed by the use of the aneroid sphygmomanometer. The cuff being firmly applied somewhere in the calf and blown up to a pressure between diastole and systole, the normal excursion of the needle with each pulse beat will be from 1.5 to 3.0 mm. An excursion of 0.5 mm. or only a trace in one leg, as compared with one of 1 or 2 mm. in the other, indicates that a large vessel is occluded at the level tested or higher. Such an observation is frequently made in thromboangiitis obliterans. When pulsations in both feet are absent, oscillometry may call attention

\*Formerly of articles in this series are not available for distribution, but the articles will be published in book form. The current volume is *U.S.A. Progress Annual, 1940* (Springfield, Illinois: Charles C. Thomas Company, 1941) \$4.00.

\*Consultant, Peter Bent Brigham Hospital and Joseph H. Pratt Diagnostic Hospital, Boston.

to a thrombosis decidedly higher in one leg than the other. The presence of a serious occlusion at some particular level may also be noted by the histamine test. Before the test is made, any overlying functional vasoconstriction should be overcome, as by gently warming the skin (with the hands). One performs the test by placing a drop of a 1:1000 solution of histamine acid phosphate on the dry, clean skin, by needling the skin several times through the drop and by feeling for a wheal. Should a wheal fail to appear in three to five minutes, the tissues are so ischemic that an incision at or below the level tested, as for amputation, is unlikely to heal. The presence or absence of a satisfactory wheal low in the leg has useful prognostic significance when the problem is not one of immediate amputation.

The worth of different vasodilatation tests, that is, of the patient's capacity for vasodilatation in response to various stimuli and to sympathetic paralysis (heating the other extremities, heating the body, administering foreign protein, sympathetic procaine block, spinal anesthesia and so forth) is discussed by Montgomery, Naide and Freeman and by Ochsner and DeBakey.<sup>2</sup> In the presence of organic arterial deficiency, these tests demonstrate the capacity of the remaining arteries for dilatation and, in general, the availability of the collateral circulation. In cases of generalized functional vascular constriction, such as is present in cyanotic, sweaty extremities, the tests recognize this state and predict relief by sympathectomy. (It should be noted that the tests may fail in two respects: they do not foretell the result of sympathectomy in improving, over a long period, the nutrition of the feet in the serious arterial deficiencies of both thromboangiitis obliterans and arteriosclerosis, and they may not relax the most serious gross arteriospasm, such as those that are rarely associated with thrombophlebitis and trauma and are subsequently discussed.)

#### *Procedures for Securing Vasodilatation*

Several methods for producing vasodilatation have recently been scrutinized, notably, intermittent venous occlusion and the administration of a number of chemicals. Intermittent venous occlusion, brought up to date through the invention of an automatic apparatus by Collens and Wilensky,<sup>3</sup> appeared capable of calling forth a reactive hyperemia. Observations of de Takats, Hick and Coulter<sup>4</sup> were confirmatory. Recently, Linton et al.<sup>5</sup> have conducted experiments revealing the immediate effects of venous obstruction on the circulation in the dog's leg. Arterial flow was measured by the *Thermostromuhr*, and venous pressures were recorded as well. Venous occlusion (clamping the principal vein) was found to increase

arterial flow to the extremity. The effect was slower, but still impressive, when the arterial supply was deficient. The increased arterial flow was found to be greater the nearer the heart the venous block was made. When a pneumatic cuff was used, each increase in tightness was followed by a rise in venous pressure and a corresponding rise in arterial flow until the tightness of the cuff reached the level of systolic pressure. Linton and his associates believe that dilatation of the venous tree primarily reduces peripheral resistance and thus permits an increased inflow from the arterial side. Possibly, arteriovenous shunts are opened. Increased arterial flow during increased venous pressure, rather than reactive hyperemia after release of the constriction, is perhaps the chief effect of *intermittent venous occlusion*. The research supports the value of the division of the principal vein of a limb when arterial occlusion has occurred.

The vasodilating effect of various drugs has been studied by Abramson et al.<sup>6</sup> They used the venous occlusion plethysmographic method, which measures the total blood flow to a portion of an extremity, and made observations on normal persons and on patients suffering from vascular and mental diseases. Calcium gluconate, Padutin, papaverine, Spasmalgin and thiamine chloride produced a slight increase or none in blood flow to the hand, forearm, leg and foot. Alcohol, stilbestrol and histamine generally increased the flow of blood to the hand only. Intravenous hypertonic saline solution augmented blood flow into the leg in only one third of the trials. This is interesting in view of the report of Silbert et al.<sup>7</sup> that the intravenous injection of 300 cc. of hypertonic (5 per cent) saline solution regularly increases blood flow to the muscles of the calf. The latter observations were recorded by the deep thermocouple rather than by methods measuring the total blood flow. One is left with the impression that increased blood flow, as induced by chemicals, is brief and of little importance.

In this connection, Brown and Allen<sup>8</sup> have devised an apparatus intended to secure prolonged vasodilatation in chronic occlusive arterial disease. Reflex vasodilatation is secured by means of a heating sleeve or boot applied to an extremity other than the one diseased. The authors believe that arteriolar dilatation is the effect chiefly secured.

#### *Use of Tobacco*

Although the smoking of tobacco has long been recognized as an aggravating factor and a cause of progressive circulatory deficiency in thromboangiitis obliterans, some recent observations are enlightening. Mulinos and Shulman,<sup>9</sup> in a study of the rate of blood flow in the hand, found that deep inhalations without smoke caused vasocon-

striction; that so-called "denicotinized" cigarettes caused a vasoconstriction like that produced by real tobacco; that the response to smoking varied greatly in different persons and in the same subject from time to time; that the actual vasoconstriction, when induced, lasted only about fifteen minutes; and that heavy smokers showed active vasoconstriction even when a systemic reaction to smoking did not take place. Hiestand et al.<sup>10</sup> observed that an increase in the pulse and basal metabolic rates usually, but not invariably, occurred in habitual smokers after the inhalation of cigarette smoke. All such observations indicate that tobacco smoking *may*, by causing vasoconstriction, unfavorably influence blood vessels, in any part of the body, that are diseased in some degree. In this respect, they are not especially impressive. The vasoconstrictive effect of tobacco is very brief. Moreover, observations of Sprague and Homans<sup>11</sup> indicate that heavy smokers suffering from thromboangiitis obliterans may benefit clinically (decided improvement in locomotion through relief of intermittent claudication) by abstinence from tobacco in the absence of Buerger's exercises or other such vasodilating influences even after preliminary observations of cutaneous temperatures in the toes have shown that inhalation of tobacco smoke causes no vasoconstriction whatsoever; and their observations confirm the general impression that abstinence from tobacco leads to recognizable clinical improvement only after many months.

Tobacco may conceivably affect the blood vessels in ways other than by vasoconstriction. Moyer and Maddock,<sup>12</sup> in reviewing the subject, recall the older observations of Harkavy, Hebal and Silbert<sup>13</sup> and of Sulzberger and Feit.<sup>14</sup> The last found that a high proportion of those suffering from thromboangiitis obliterans reacted positively to intradermal injections of various extracts of tobacco (even when nicotine was removed) and not to nicotine itself. Harkavy et al. made similar observations on tobacco-smoking patients who had Buerger's disease, with the additional finding that other smokers rarely so reacted. Since there is reasonably acceptable proof that those who have never smoked occasionally suffer from thromboangiitis obliterans, the question arises whether tobacco acts directly or whether it may not rather reinforce the patient's sensitivity to another adverse influence, such as the presence of a dermatophytosis.

#### *Significance of Dermatophytosis*

Thompson<sup>15</sup> suggests that a number of familiar vascular diseases,—namely, thrombophlebitis, phlegmasia alba dolens, migrating phlebitis,

thromboangiitis obliterans and postphlebotic ulcer,—seemingly unrelated, have a common background of "endothelial necrosis, thrombosis and chronic inflammation involving the walls of blood vessels and their adjacent tissues." With these disorders, the dermatophytoses of the feet are invariably\* associated. Drawing a comparison with tuberculosis, he shows how allergic reactions to antigens derived from the fungi may well constitute the basis of these various lesions. From patients suffering with Buerger's disease and various leg ulcers, he has cultivated fungi from which he<sup>16</sup> has secured a powerful antigen. This antigen provokes in the skin of the legs of persons with such diseases (and not in persons free from them) vivid cutaneous reactions following the intradermal injection of infinitely small doses. Thompson's observations are, of course, in the experimental stage.

Whether or not this line of investigation will prove fruitful and whether or not smoking aggravates supposed allergic reactions of this sort, there is no doubt that effective treatment of dermatophytosis and onychomycosis, combined with abstinence from smoking, has proved of great value in the treatment of thromboangiitis obliterans and other peripheral vascular diseases.

#### *Intermittent Claudication*

With the aid of a mechanical device for studying the ability of the muscles of the calf to contract (Hitzrot, Naide and Landis<sup>17</sup>), Freeman and Montgomery<sup>18</sup> have investigated the effect of sympathetic block and sympathectomy on claudication. They found that when a considerable element of abnormal vasoconstriction was present, as indicated by moist, bluish feet and contracted veins, sympathectomy improved the ability of the muscles to work and increased the walking distance. By selecting their cases of both arteriosclerosis and thromboangiitis obliterans on the basis of a favorable reaction to preliminary sympathetic procaine block, they were able to secure a decided improvement in walking. Undoubtedly, the writers prove their point in respect to a favorable effect in selected cases. But that is not to say that one may not see considerable gradual improvement in locomotion as a result of abstinence from tobacco, scrupulous care of the feet and Buerger's exercises (about which combination the writers say almost nothing). Moreover, observations of Wallace and Smithwick,<sup>19</sup> based on a long series of sympathectomies in serious obliterative vascular disease, show that, even in the absence of a favorable reaction to sympathetic block, sympathectomy

\*On a purely clinical basis, yet without proof by the demonstration that pathogenic fungi are present in the skin



causes, over a considerable period, significant clinical improvement (including locomotion) in a great majority of cases.

### VASOCONSTRICTIVE AND VASOSPASTIC DISEASES

In the second edition of their excellent monograph, *The Autonomic Nervous System*, White and Smithwick<sup>20</sup> decline to differentiate classic Raynaud's disease and such allied vasospastic conditions as acrocyanosis. They group together the acute, recurrent vasospasms in the extremities, regarded by most observers as Raynaud's disease, with the continued vasoconstrictions, — in fact, all the sympathetic dysfunctions remediable by sympathectomy. This is not in accordance with the usual practice in this country, the definition of Raynaud's disease being decidedly narrow, and excluding all vasoconstrictions and vasospasms except the recurrent spasms of the digital arteries as a reaction to cold and emotion. In this review, Raynaud's disease, in the sense of a vasospastic disorder causing acute attacks of cyanosis or asphyxia of the fingers (and toes) on a background of reasonable normalcy, will not be considered. Smithwick<sup>21</sup> discusses it fully in a recent review of the sympathetic system.

#### *Acrocyanosis*

This vague term may properly be applied to the very common reddish-blue, moist extremity. It is difficult to discern the borderline between a richly pink, moist hand and a cyanotic, wet one. In each, there seems to be an exaggerated vasomotor tone in the smaller blood vessels, presumably the arterioles. Social conditions, occupation and self-consciousness or the lack of it make some acrocyanoses and hyperhidroses pathologic, others not.

White,<sup>22</sup> in a picturesque account, strongly recommends preganglionic sympathectomy for hyperhidrosis, since he found no effective palliative treatment.

Regarding acrocyanosis as it commonly occurs in girls and young women, a condition worse in the feet of some patients and in the hands of others, no new information is at hand. The rubor or cyanosis is made worse by cold. White and Smithwick<sup>20</sup> point out that ultimately, in occasional patients, Raynaud's phenomenon of acute, recurrent vasospasm may be superimposed. The background of exaggerated vasomotor (constrictor) tone seems to be curable only by sympathectomy. Recently, several related varieties of acrocyanosis have received attention: namely, livedo reticularis and pernio or erythrocyanosis frigida.

#### *Livedo Reticularis*

This is described as a peripheral arteriolar disease by Barker, Hines and Craig.<sup>23</sup> In their cases,

the upper and lower limbs were covered with purplish discolorations having various forms: hence the terms, "livedo racemosa," "livedo annularis" and "cutis marmorata." The disease, an uncommon one, was seen equally often in men and women. The extremities, especially the fingers, toes, hands and feet, were subjectively and objectively cold and sometimes painful. The large vessels and peripheral pulsations were normal.

The livid areas, as these and other writers have observed, are most marked and thickly distributed peripherally, gradually becoming less colored as the trunk is approached. They are very persistent, and any one spot is only momentarily whitened by pressure. Warmth turns them toward red or pink. Even a sympathetic block is powerless to make them disappear. Organic changes — perivascular lymphocytic infiltration and fibrosis — were found by Barker et al. to be present in the arterioles, and in occasional cases, serious gangrene of the toes was noted. No etiologic factor is known. Treatment by sympathectomy is justifiable.

#### *Pernio*

Pernio, erythrocyanosis frigida and many similar names have been given to the condition commonly referred to as "chilblain," in which a state of peripheral cyanosis is complicated by purplish, raised indurations that ulcerate. McGovern, Wright and Kruger<sup>24</sup> give a thorough résumé of the literature and an authoritative account of the disorder. As in Bazin's disease (erythema induratum), the ulcerations occur principally in the legs of girls. But here, the girls are well nourished, even fat, whereas the victims of Bazin's disease are ill nourished and supposedly tuberculous. In fact, Bazin's disease is believed to be a tuberculid, whereas pernio presents no characteristic pathology.

The authors describe 10 cases, with full reports and with sections of some of the ulcers. The disease, which predominated in young women, appeared in the early winter and disappeared in the spring. The patches, at first red, soon became elevated, hard, purple and painful. They then broke down in part, forming chronic ulcers. Angiitis of the small vessels beneath the ulcers was noted. Although the lower legs were involved in this group, others have noticed similar lesions in the upper extremities when these parts were exposed and the legs were not.

Treatment with acetyl-betamethylcholine chloride (Mecholyl) by iontophoresis and protection from cold are recommended. No mention is made of sympathectomy, of which others spoke in a discussion of the communication and which has been used with apparent success (Homans<sup>25</sup>).

### Frostbite

In connection with pernio, the observations of Leriche and Kunlin<sup>26</sup> on frostbite as a "vasomotor and thrombotic disease" are perhaps appropriate. Following various degrees of frostbite, some digits were found to be edematous and blistered, with raised, loosened nails, while others became gangrenous. Even when edema had disappeared and healing had occurred, painful arterial constriction and even intermittent claudication often remained. Such states were helped by repeated sympathetic procaine block. The authors recommend that the early stages of frostbite and chilblain, marked by edema and pain, be treated by sympathetic procaine block. Such treatment, in their hands, rapidly relieved cases in which there was no actual necrosis, and was of benefit to all patients.

### ARTERIAL SPASM AND ARTERITIS

#### Traumatic Arterial Spasm

Gross spasm of a temporary or prolonged sort in response to various stimuli is becoming reasonably well understood. The larger arteries of the limbs are most frequently involved. Foisie<sup>27</sup> has recently discussed this subject and has called attention to Griffiths's<sup>28</sup> work on Volkmann's contracture. As a result of a number of surgical explorations, Griffiths opposes the conception that this crippling results from an acute venous engorgement due to hemorrhage within the muscular aponeurosis. The disorder is commonest after supracondylar fractures at the elbow. Tight bandages and acute flexion have been thought to be aggravating factors. Griffiths holds that weakening or loss of the radial pulse is the earliest evidence that trauma has thrown the brachial artery into spasm. His explorations revealed a local contraction of the brachial artery that transmitted a mere trickle of blood, a finding identical with an earlier observation of Montgomery and Ireland.<sup>29</sup> His best results followed resection of the spastic vessel, but he suggests that, in cases of moderate severity, immobilization and the administration of papaverine may be effective. Stripping the artery has not been successful, nor has sympathetic procaine block.

One should be on the lookout for this lesion when loss of the peripheral pulses and threatened gangrene of some of the digits follow a bullet wound that has not actually divided an artery, or even when they follow such an apparently trivial injury as the insertion of a needle, during venipuncture, into the cubital space.

In this connection, Leriche and Werquin,<sup>30</sup> have recently called attention to the favorable effect of dividing an injured artery or resecting a considerable portion of it, as opposed to ligation in con-

tinuity. The chances of securing an effective collateral circulation are greatly improved by resection, an old contention of Leriche's, especially applicable in war surgery when arteries are likely to be extensively lacerated and thrombosed in complicated wounds. Resection tends to break up reflex vasoconstriction originating in irritation of the arterial wall and favors the development of a collateral circulation.

#### Arteritis

Hoyt, Perera and Kauvar<sup>31</sup> report 3 cases of temporal arteritis, a lesion first described by Horton, Magath and Brown.<sup>32</sup> This unexplained granulomatous, inflammatory disease of the temporal arteries in elderly persons is associated with serious headache and constitutional symptoms of a severity out of all proportion to the local lesion and tenderness, with redness, over the temporal vessels. No underlying causative factor has consistently been noted. In their cases, resection of a portion of the diseased artery relieved pain and favorably influenced the disease, but fever generally continued for several weeks.

#### Arterial Spasm Resulting from Cervical Rib (Scalenus Syndrome)

MacFee<sup>33</sup> calls attention to dilatation of the subclavian artery distal to the point at which it is compressed behind the scalenus anticus muscle. He found 125 cases with vascular symptoms among 360 cases of cervical rib with pressure symptoms (either nervous, vascular or both). In the particular case he describes, the brachial artery was also noted as a hard pulseless cord. Several fingertips of the cyanotic hand were gangrenous. This account recalls a very similar case reported by Cluie<sup>34</sup> as being "acute arterial obstruction from arteritis." A very reasonable explanation of these peculiar findings has been offered by Telford and Stopford,<sup>35</sup> who suggest that irritation of the vasomotor nerves in the lowest cord of the brachial plexus as it passes over the first or a cervical rib is responsible for spasm and subsequent closure of the brachial artery, and it must be supposed that dilatation of the subclavian is part of the reaction. Besides freeing the structures behind the scalenus anticus muscle, the hard, cordlike brachial artery should probably be resected.

#### Arterial Spasm in Thrombophlebitis

The French and German literature since 1934 has contained accounts of arterial spasms that rarely occur with the onset of femoral thrombophlebitis yet may be serious enough to produce gangrene of the leg. The cause of such spasms, as Leriche and Kunlin<sup>36</sup> have suggested, lies in a perivascular irritation that not only throws the

adjacent artery into contraction but sets up a reflex peripheral vasoconstriction, which will be discussed in the section on thrombophlebitis. The onset of phlegmasia alba dolens is often marked by a diminution in the femoral and peripheral pulses. Rarely, all pulsations below the inguinal ligament disappear, the leg becoming white and cold, as if arterial embolism had occurred. Should the spasm persist, gangrene sets in. Should it relax, as it may very suddenly do, the whole leg becomes engorged with blood. Sympathetic block seems to have little influence on the more violent spasms, although it undoubtedly causes the milder ones to relax.

(To be concluded)

## REFERENCES

1. Montgomery, H., Naide, M., and Freeman, N. E. The significance of diagnostic tests in the study of peripheral vascular disease. *Am. Heart J.* 21:780-803, 1941.
2. Ochsner, A., and DeBakey, M. The rational consideration of peripheral vascular disease based on physiologic principles. *J. A. M. A.* 112:230-236, 1939.
3. Collens, W. S., and Wilensky, N. D. An apparatus for the production of intermittent venous compression in the treatment of peripheral vascular disease. *Am. Heart J.* 11:721, 1936.
4. de Takats, G., Hick, F. K., and Coulter, J. S. Intermittent venous hyperemia in the treatment of peripheral vascular disease. *J. A. M. A.* 108:1951-1959, 1937.
5. Linton, R. R., Morrison, P. J., Ulfelder, H., and Libby, A. L. Therapeutic venous occlusion: its effect on the arterial inflow to an extremity, as measured by means of the Rein thermistoruhr. *Am. Heart J.* 21:721-742, 1941.
6. Abramson, D. I., Zazeela, H., and Schkloven, N. The vasodilating action of various therapeutic procedures which are used in the treatment of peripheral vascular disease. *Am. Heart J.* 21:756-766, 1941.
7. Friedlander, M., Silbert, S., and Bierman, W. Regulation of circulation in the skin and muscles of the lower extremities. *Am. J. M. Sc.* 199:657-668, 1940.
8. Brown, G. E., Jr., and Allen, E. V. Continuous vasodilatation in the extremities produced reflexly: physiologic studies on temperature of skin and on volume flow of blood. *Am. Heart J.* 21:564-573, 1941.
9. Mulinos, M. G., and Shulman, I. The effects of cigarette smoking and deep breathing on the peripheral vascular system. *Am. J. M. Sc.* 199:708-720, 1940.
10. Hiestand, W. A., Ramsey, H. J., and Hale, D. M. The effects of cigarette smoking on metabolic rate, heart rate, oxygen pulse, and breathing rate. *J. Lab. & Clin. Med.* 25:1013-1017, 1940.
11. Sprague, J. S., and Homans, J. Unpublished data.
12. Moyer, C. A., and Maddock, W. G. Peripheral vasospasm from tobacco. *Arch. Surg.* 40:277-285, 1940.
13. Harkavy, J., Hebal, S., and Silbert, S. Tobacco sensitiveness in thromboangiitis obliterans. *Proc. Soc. Exper. Biol. & Med.* 30:104-107, 1932.
14. Sulzberger, M. B., and Feit, E. Studies in tobacco hypersensitivity. I. A comparison between reactions to nicotine and to denicotinized tobacco extract. *J. Immunol.* 24:85-91, 1933. II. Thromboangiitis obliterans with positive urticarial skin reactions and negative reagin findings. *Ibid.* 24:425-432, 1933.
15. Thompson, K. W. The relationship of the dermatomycoses to certain peripheral vascular infections. *New Internat. Clin.* 2:156-170, 1941.
16. *Idem*. Personal communication.
17. Hitzrot, L. H., Naide, M., and Landis, E. M. Intermittent claudication studied by a graphic method. *Am. Heart J.* 11:513-526, 1936.
18. Freeman, N. E., and Montgomery, H. Lumbar sympathectomy in the treatment of intermittent claudication: selection of cases by claudication test with lumbar paravertebral procaine injection. *Am. Heart J.* 23:224-242, 1942.
19. Wallace, R. H., and Smithwick, R. H. Unpublished data.
20. White, J. C., and Smithwick, R. H. *The Autonomic Nervous System: Anatomy, physiology, and surgical application*. Second edition. 469 pp. New York: Macmillan Co., 1941. P. 185.
21. Smithwick, R. H. Surgery of the autonomic nervous system: method of study, with particular reference to the interpretation of clinical results. *New Eng. J. Med.* 126:605-612, 1942.
22. White, J. C. Hyperhidrosis of nervous origin and its treatment by sympathectomy. *New Eng. J. Med.* 220:181-186, 1939.
23. Barker, N. W., Hines, E. A., Jr., and Craig, W. McK. Livedo reticularis: a peripheral arteriolar disease. *Am. Heart J.* 21:592-604, 1941.
24. McGovern, T., Wright, I. S., and Kruger, E. Pernio: a vascular disease. *Am. Heart J.* 22:583-606, 1941.
25. Homans, J. *Circulatory Diseases of the Extremities*. 330 pp. New York: Macmillan Co., 1939. P. 149.
26. Leriche, R., and Kunlin, J. Physiologie pathologique des gelures, maladie d'abord vaso-motrice, puis thrombosante. *Progrès méd.* 68:169-173, 1940.
27. Foise, P. S. Volkmann's ischemic contracture: an analysis of its proximate mechanism. *New Eng. J. Med.* 226:671-679, 1942.
28. Griffiths, D. L. Volkmann's ischaemic contracture. *Brit. J. Surg.* 28:239-260, 1940.
29. Montgomery, A. H., and Ireland, J. Traumatic segmentary arterial spasm. *J. A. M. A.* 105:1741-1746, 1935.
30. Leriche, R., and Werquin, M. G. Effects of arterial ligation on the vasomotor system. *Lancet* 2:296, 1940.
31. Hoyt, L. H., Perera, G. A., and Kauvar, A. J. Temporal arteritis. *New Eng. J. Med.* 225:283-286, 1941.
32. Horton, B. T., Magath, T. B., and Brown, G. E. Arteritis of the temporal vessels: a previously undescribed form. *Arch. Int. Med.* 53:400-409, 1934.
33. MacFée, W. F. Cervical rib causing partial occlusion and aneurysm of the subclavian artery. *Ann. Surg.* 111:549-553, 1940.
34. Clute, H. M. Acute arterial obstruction from arteritis. *New Eng. J. Med.* 214:137-140, 1936.
35. Telford, E. D., and Stopford, J. S. B. The vascular complications of cervical rib. *Brit. J. Surg.* 18:557-564, 1931.
36. Leriche, R., and Kunlin, J. Traitement immédiat des phlébites post-opératoires par l'infiltration novocaïnique du sympathique lombaire. *Presse méd.* 42:1481, 1934.

CASE RECORDS OF THE  
MASSACHUSETTS GENERAL HOSPITALANTE-MORTEM AND POST-MORTEM RECORDS AS USED  
IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

## CASE 28231

## PRESENTATION OF CASE

*First admission.* A sixty-two-year-old single female physician was admitted to the hospital because of fever for a day following an intermittent cough of a month's duration.

Four weeks before entry, the patient had a sore throat followed in a few days by a dry hacking paroxysmal cough. The cough persisted when the soreness in the throat subsided. About a week later, the cough grew worse during the course of another few days of sore throat. The night before entry, the patient had a severe paroxysm of coughing, "wheezing on inspiration like an asthmatic." This was followed by a chill lasting three hours. She felt nauseated but did not vomit. Soreness but no actual pain developed in the right chest and was aggravated by respiration. The next day, fever was noted, and she entered the hospital.

The patient had been in the hospital five times before, with symptoms suggesting cholecystitis and renal colic. Six years before the last entry, operation disclosed right hydronephrosis due to aberrant blood vessels. These vessels were ligated, and a right nephropexy was performed. At a second operation several months later, an acutely inflamed gall bladder with a single stone was removed. These operations afforded complete relief from symptoms. Four years before the last entry, the patient had a sudden attack of severe "anginoid pain" radiating up the left side of the neck and down the left arm. This attack, which began when the patient was in bed, lasted half an hour. Dull pain and soreness remained for about three days after the acute phase. Three years before entry, there was a similar attack. This episode was not preceded by exertion. After this, the patient remained symptom free except for momentary "tight" sensations beneath the sternum "on climbing hills."

On admission, the patient appeared obese and uncomfortable, with a dry hacking cough. The hands were somewhat cyanotic. The lungs seemed clear. The heart was not remarkable.

The blood pressure was 130 systolic, 60 diastolic. The temperature was 102°F., the pulse 110, and the respirations 30.

Examination of the blood showed a white-cell count of 36,000. The blood Hinton reaction was negative. The urine showed occasional red and white cells in the sediment but was otherwise normal. Throat culture grew beta-hemolytic streptococci but no pneumococci. A blood culture was sterile.

A roentgenogram of the chest showed moderate prominence of the lung roots, without definite evidence of pneumonia.

The patient was given sulfadiazine for five days, a maximum blood level of 18 mg. per 100 cc. being attained on the second day. The temperature returned to normal on the third day, and there was a corresponding fall in the white-cell count to normal. The patient was discharged improved on the tenth hospital day.

*Final admission* (two weeks later). The patient remained well until five days before re-entry, when there was sudden onset of chills and fever, with severe shaking and profuse sweating. The fever was intermittent, reaching 104 or 105°F. each day. The right flank and right upper quadrant became tender. There was no headache, nausea or vomiting.

On readmission, the patient was too tired to sit up for examination. A few crepitant rales were audible at the end of inspiration over the left upper chest anteriorly and posteriorly. The heart seemed normal except for a slight systolic murmur at the apex. There was some tenderness in the left lower quadrant of the abdomen, seemingly over the sigmoid and descending colon. Posteriorly, there was tenderness over the lumbar spine and slight tenderness in the costovertebral angle on each side.

The blood pressure was 100 systolic, 60 diastolic. The temperature was 98°F., the pulse 98, and the respirations 20.

Examination of the blood showed a white-cell count of 26,400 with 95 per cent polymorphonuclears, 4 per cent lymphocytes and 1 per cent monocytes; no parasites were seen in stained smear. Agglutination tests for typhoid fever and undulant fever were negative. The nonprotein nitrogen was 41 mg. per 100 cc. The urine showed a + test for albumin and occasional red and white blood cells in the sediment. Urine and stool cultures grew no significant pathogenic organisms.

A roentgenogram of the abdomen showed considerable gas in the colon and a dilated loop of bowel consistent with ileum in the right mid-abdomen. A roentgenogram of the chest showed no definite evidence of pulmonary consolidation or of pleural effusion. A roentgenogram of the left shoulder was negative. An intravenous pyelo-

DR. LYONS: This whole business of hepatitis is a problem of much interest. We studied 68 patients last spring by prothrombin levels and bromsulfalein retention, and found that 20 per cent of those receiving chemotherapy for acute infection developed some evidence of impaired prothrombin time or bromsulfalein retention and that jaundice was not a regular accompaniment. That type of hepatic disturbance remains to be elucidated.

#### CLINICAL DIAGNOSIS

Acute bacterial endocarditis, Type 7 pneumococcus.

#### DR. ROPES'S DIAGNOSES

Pneumococcal endocarditis.

Ureteral obstruction from sulfadiazine crystals.

#### ANATOMICAL DIAGNOSES

Endocarditis, bacterial (Type 7 pneumococcus).

Renal infarction, complete, right kidney.

Splenic infarction, small.

Nephritis, focal glomerular, acute.

Arteriosclerosis, aortic and coronary, minimal.

Operative scars: nephropexy, cholecystectomy.

#### PATHOLOGICAL DISCUSSION

DR. MALLORY: Post-mortem examination did show a pneumococcal endocarditis of the mitral valve. There was a very large vegetation, 2 cm. in diameter, on the right cusp. This had evidently given off emboli, and one of considerable size was found in the right renal artery, so that the right kidney was totally infarcted. There was also an infarct in the spleen. The left kidney was somewhat swollen. It was examined with great care for crystals. None could be found in the pelvis or the ureter on that side. On the other hand, some crystals were seen in the pyramid. These were teased out, but did not look like the crystals of any of the sulfonamides and proved to be urates. The glomeruli in this case were also abnormal. The glomerulonephritis was somewhat uneven in distribution—very marked in some glomeruli and relatively less marked in others. Of course, glomerular involvement can occur with any form of bacterial endocarditis, so that this is perhaps to be regarded as a very diffuse form of so-called "embolic glomerulonephritis" rather than a true diffuse glomerulonephritis.

The coronary arteries were entirely normal, and there was no hiatus hernia; nothing else was found to explain the attacks of anginal pain. The liver was slightly large and mottled, but showed no demonstrable hepatitis.

#### CASE 28232

#### PRESENTATION OF CASE

A forty-three-year-old shipping clerk was admitted to the hospital because of vomiting and associated abdominal cramps.

He was well until about eight weeks before entry, when he was awakened from sleep by severe cramping pain in the upper abdomen. He vomited part of his supper, together with some peanuts that he had eaten shortly before retiring an hour and a half earlier. There was no further difficulty until two weeks later, when the patient was again seized with severe, shooting epigastric cramps and vomited peanuts eaten an hour earlier. The vomiting was spontaneous and was not accompanied by nausea. It relieved the pain promptly. A physician prescribed belladonna and Amphogel, with restriction of the diet. Subsequently, the patient vomited two or three times a week, with associated pain but no nausea as before. He felt weak and therefore stopped working. He was referred to the Out Patient Department, where physical examination was essentially negative. Roentgenograms of the esophagus, stomach, duodenum and small bowel were likewise negative. The patient was advised to continue his dietary restrictions and his medication. In the four weeks preceding entry, the vomiting became more frequent and severe. The patient often vomited greenish bitter fluid an hour or an hour and a half after breakfast and after lunch. In the week before entry, such vomiting and abdominal cramps followed every meal. Small amounts of bright-red blood were spat up after vomiting. The patient lost 20 pounds of weight during the illness.

The appendix had been removed six years before entry. The past history was otherwise irrelevant.

On admission, the heart and lungs were normal. The abdomen showed slight deep epigastric tenderness but no masses or palpable viscera. Rectal palpation was essentially negative.

The blood pressure, temperature, pulse and respirations were normal.

Examination of the blood showed a red-cell count of 4,600,000 with 85 per cent hemoglobin, and a white-cell count of 8700 with 64 per cent polymorphonuclears. The serum protein was 6.5 gm. per 100 cc. The chlorides were 85.6 milliequiv. per liter, rising to 98.5 milliequiv. Gastric analysis showed 8.0 units of free acid and 9.5 units of total acid (fasting), with no appreciable increase after histamine. The stools were strongly positive for occult blood. The urine was normal.

A roentgenogram of the abdomen showed old residual flecks of barium in the lower descending

colon, possibly in diverticulums. There was considerable gas in the stomach. A repeat roentgenologic examination of the gastrointestinal tract showed a normal esophagus and stomach. The second portion of the duodenum was somewhat dilated, and there was slight delay at the junction of the second and third portions of the duodenum. The third portion was poorly filled and included a crater 1 cm. across, with surrounding induration and probable mucosal destruction. There were several intraluminal defects in the left half of the large bowel suggesting either fecaliths or polyps. On the ninth hospital day, an operation was performed.

### DIFFERENTIAL DIAGNOSIS

DR. JOHN R. GRAHAM: The final x-ray pictures have shown us a definite lesion in the third portion of the duodenum, although the first series failed to reveal any abnormalities. It seems to me that a lesion in this situation would adequately explain the symptoms of vomiting and epigastric pain. The ulcerations mentioned in the last x-ray report could explain the positive guaiac test in the stools, although one would have to think that the patient could not have had a strongly positive guaiac test for very long without more anemia than the blood count showed.

DR. GEORGE W. HOLMES: The fact that they had taken a number of films of this area showed that they were interested in it. The obstruction at the lower portion of the duodenal loop where it joins the ileum is obvious in a number of films, all of which show barium delayed at that point. I suspect that this is what they thought was the ulcer. There is also an unusual amount of gas in the small bowel in some of the films. The colon is normal. The stomach, so far as I can see, is normal. From the evidence I have here, one can say only that there was a definite delay in the passage of the barium meal from the duodenal loop into the jejunum. In one film, it looks like an ulcer.

DR. GRAHAM: Between the duodenal loop and the jejunum?

DR. HOLMES: Yes.

DR. GRAHAM: As I have said, I think the lesion explains the symptoms, and my job is to guess the histology of the lesion. It has certain characteristics, which we can learn from the history and the x-ray pictures. The x-ray films tell us that the lesion was ulcerative, that it had an area of induration around it, and that the mucosal pattern of the bowel showed evidence of being destroyed. I think those things suggest the presence of a malignant lesion, probably one arising in the bowel itself. There is evidence, in the history and perhaps in the x-ray examination, that this lesion progressed

rather rapidly. The whole illness lasted only eight weeks, the symptoms and signs growing rapidly worse during the course of the last month. The x-ray films taken at the end of one month of symptoms failed to reveal dilatation or evidence of obstruction or any lesion that could be seen, whereas those taken after two months of symptoms showed definite trouble. Further evidences against an inflammatory lesion were the normal temperature and the normal white-cell count. The x-ray report mentioned the possible presence of polyps in the colon, which suggest that the patient might have had polyps elsewhere, even in the duodenum. Dr. Holmes, however, doubts the evidence of polyps.

I think the main thing to think of in identifying this lesion is whether it was a carcinoma of the duodenum near the junction of the jejunum, or a lymphoma. We also have to think about a peptic ulcer, since an ulcer was definitely demonstrated. It seems to me that the location of the lesion, the low gastric acidity and the duration of the symptoms are distinctly against an ordinary duodenal or peptic ulcer. One would think about syphilis, but they probably would have helped us out with the Hinton report. There was no history of syphilis. Could the condition have been regional enteritis? On the whole, I lean away from an inflammatory lesion and think that the most likely diagnosis is a carcinoma in that part of the bowel. The second on my list is lymphoma, and I shall simply mention in passing the possibility of polyp that has undergone malignant degeneration, the only reason for that thought being the doubtful presence of polyps elsewhere in the intestinal tract.

DR. CHESTER M. JONES: It seems to me that the first x-ray film did not show anything because it was routine. I think that is a fair statement, but I should like to have Dr. Holmes comment on it. Very frequently, unless the radiologist is asked to look for a definite lesion, he may on routine examination overlook a lesion in the third portion of the duodenum. This lesion may well have been there a month before.

DR. HOLMES: I agree with you, and should like to emphasize the fact that clinicians should tell the radiologist what they have in mind before asking for the x-ray report. One does not see things one does not look for.

DR. JONES: I have seen only a small number of cases of cancer of the terminal ileum, upper jejunum or the lower duodenum. With the history, not of epigastric pain but of umbilical pain, one is given the clue. The lesion should lie in the small bowel well below the mid-duodenum, and one has the right to ask Dr. Holmes to look for it.

DR. GRAHAM: One must consider the possibility of a malignant lesion, extrinsic to the bowel, something to do with the pancreas. However, I thought that the directness with which the symptoms were connected with the lesion and the ulceration were against that.

DR. TRACY B. MALLORY: Can you say anything from the x-ray point of view concerning the possibility of pancreatic tumor?

DR. HOLMES: I think it is a decided possibility; narrowing and obstruction in that part of the duodenum not infrequently are due to cancer arising in the pancreas. The absence of a gross deformity of the duodenal loop does not rule out cancer of the pancreas. I used to think a deformed loop was necessary. But that is not so.

#### CLINICAL DIAGNOSIS

Duodenal cancer?

#### DR. GRAHAM'S DIAGNOSIS

Carcinoma of duodenum.

#### ANATOMICAL DIAGNOSIS

Carcinoma of pancreas, invading duodenum.

#### PATHOLOGICAL DISCUSSION

DR. MALLORY: This patient was explored, and a localized tumor was found in the pancreas in about the midportion. It had invaded the duodenal wall and had produced a small papillary mass in the duodenum, but no ulcer that I could find. A gastroenterostomy was done, and a biopsy of the pancreas showed perfectly normal pancreatic tissue. However, the patient did not long survive gastroenterostomy, and at post-mortem examination we were able to confirm the diagnosis of cancer in the pancreas.

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established in 1828

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND  
PUBLISHED UNDER THE JURISDICTION OF THE  
COMMITTEE ON PUBLICATIONS

Official Organ of

THE MASSACHUSETTS MEDICAL SOCIETY  
and  
THE NEW HAMPSHIRE MEDICAL SOCIETY

## EDITORIAL BOARD

Joseph Garland, M.D.	Stephen Rushmore M.D.
William B. Breed, M.D.	Henry R. Vieta, M.D.
George R. Minot, M.D.	Robert M. Green, M.D.
Frank H. Lahey, M.D.	Charles C. Lund, M.D.
Sheldie Warren, M.D.	John F. Fulton, M.D.
George L. Tobey, Jr., M.D.	A. Warren Stearns, M.D.
C. Guy Lane, M.D.	Dwight O. Hara, M.D.
William A. Rogers, M.D.	Chesler S. Keefe, M.D.

## ASSOCIATE EDITORS

Thomas H. Lanman, M.D.	Donald Munro, M.D.
Henry Jackson, Jr., M.D.	

Walter P. Bowers, M.D., EDITOR EMERITUS

Robert N. Nye, M.D., MANAGING EDITOR

Clara D. Davies, ASSISTANT EDITOR

**SUBSCRIPTION TERMS** \$6.00 per year in advance, postage paid for the United States (medical students, \$3.50 per year); Canada, \$7.04 per year; Boston Union, \$8.52 per year for all foreign countries belonging to the Postal Union.

**MATERIAL** for early publication should be received not later than noon on Friday.

**THE JOURNAL** does not hold itself responsible for statements made by any contributor.

**COMMUNICATIONS** should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston, Massachusetts.

## MEDICAL OFFICERS' RECRUITING BOARD

The office of the Medical Officers' Recruiting Board of Massachusetts is located at 319 Longwood Avenue, Boston (telephone, ASP 3638); all physicians who desire commissions as medical officers in the Army of the United States should immediately communicate with the officers in charge.

## ANNUAL MEETING

THE one hundred and sixty-first annual meeting of the Massachusetts Medical Society, held May 25, 26 and 27 at the Hotel Statler, Boston, resulted in the largest registration of members, 1556, in the history of the Society, in spite of the fact that several hundred of those who, in the past, have

regularly attended these meetings are now away from Massachusetts, serving as medical officers in the United States Army and Navy. The luncheon meetings of the sections were well attended, but there was a distinct drop in the registration of wives, undoubtedly owing to the limitations to the program arranged by the Ladies' Committee that were necessitated by lack of transportation facilities. Never before have there been so many scientific and technical exhibits; the Ballroom and Ballroom Assembly of the Hotel Statler, however, are so well adapted for exhibits of this sort that both the members and the exhibitors were more than pleased with the arrangement.

The new schedule calling for the annual meetings of the supervising censors and of the Council during the late afternoon and evening of the day preceding the opening of the general sessions worked out very satisfactorily. The main items of business at the meeting of the Council comprised reports of the standing and special committees and the appointment of new committees. The following officers were elected for the year 1942-1943: president-elect, Roger I. Lee, of Boston; vice-president, Peirce H. Leavitt, of Brockton; secretary, Michael A. Tighe, of Lowell; treasurer, Charles S. Butler, of Boston; and orator, Edward P. Bagg, of Holyoke. Some controversy arose concerning the procedure to be adopted regarding graduates of approved medical schools who are in or about to enter the United States Army or Navy and who desire to become members of the Society; the matter was referred to the recessed meeting of the Council on the following day, and at that time, the Society, at its annual meeting, having voted to waive, for the duration of the present emergency, the by-laws relating to the timetable governing applications for membership from such graduates, two physicians whose applications were irregular were admitted to membership. At the same recessed meeting, Dr. Eliot Hubbard, Jr., of Cambridge, was elected assistant treasurer.

The annual meeting of the Society was unusually long, chiefly owing to considerable discussion concerning the proposed by-laws. Several members



opposed two of the regulations—that requiring five-year licensure in the United States before a graduate of a foreign medical school can apply for membership in the Society and that specifying that the Committee on Nominations shall cause its report to be published in the notice of the annual meeting of the Council; however, both these sections were passed by a vote of hands, and all the others by practically unanimous consent. At the close of the business meeting the incoming president, Dr. George Leonard Schadt, of Springfield, was introduced. Following the meeting, Dr. William B. Castle, of Boston, delivered the annual oration, “Some Remarks on Therapy for Anemia,” which appears elsewhere in this issue of the *Journal*.

Dr. Frank H. Lahey, of Boston, president of the American Medical Association, and Dr. Morris Fishbein, of Chicago, editor of the *Journal of the American Medical Association*, were the speakers at the annual banquet, which was attended by over 500 members and guests. Both emphasized the great need for young physicians in the armed forces, urged all under forty-five years of age to volunteer and warned that conscription will inevitably follow if the voluntarily enlisting personnel proves insufficient. The banquet was followed by the Shattuck Lecture, “Medicine and Air Supremacy.”\* The speaker, Dr. John F. Fulton, of New Haven, Connecticut, stressed the role that medicine has played in the development of combat aviation, particularly regarding the problems brought about by high-altitude flying, crashes and the care of pilots after injury; he predicted that within a year nearly twenty thousand flight surgeons and aviation medical officers will be needed in the Army Air Forces.

The majority of the papers read at the general sessions concerned one or another aspect of medicine as applied to the present emergency. Various problems of civilian defense were discussed, and mumps, tropical diseases, venereal diseases, skin diseases, head injuries, industrial health and mass immunization were considered in relation to the war effort. Other speakers commented on the effects of the war on public-health problems, medi-

cal education and American medicine in general, and the program was concluded by a symposium covering minor psychiatric disturbances in war and in civilian life.

All in all, the meeting was eminently successful, and one that will be remembered for many years by those who attended.

\*Fulton, J. F. Medicine and air supremacy. *New Eng. J. Med.* 226:573-880, 1942.

## THE COMMONWEALTH FUND

IN its twenty-third annual report, the Commonwealth Fund gives an account of its current effort to “do something for the welfare of mankind,” in accordance with the wish of its founder, Mrs. Stephen V. Harkness. A total of \$1,841,332 was appropriated for philanthropic purposes during the past year.

The policy of the fund paralleled that of previous years, in spite of adjustments made necessary by the war. Although the British fellowships offered since 1925 were suspended, although many members of nursing and medical staffs aided by the fund were called to military duty, and although a research project that had made great contributions to the knowledge of kidney function was halted because key workers went into national service, most of the undertakings progressed toward the goal of health maintenance and scientific advance. Subsidies and consultant services were furnished in twenty-eight states to encourage research and high standards of teaching in medical schools, to enrich and extend rural health services, to provide or improve hospital facilities in rural districts, and to furnish and reinforce community opportunities for mental-health services. The fund subsidized departments of preventive medicine at five medical schools and a department of psychiatry at another. A grant was made to the Peter Bent Brigham Hospital in Boston for the enlargement of its psychiatric service.

Since the war began, the fund has contributed \$685,000 for war relief and related activities. An epidemiologic unit, maintained by the fund in co-operation with Harvard University and the American Red Cross, is operating a hospital and field service for the control of communicable disease in England. And, through the British War Re-

of Society, support of the American Hospital in Britain has been maintained. The mental health services for children, provided through the Child Welfare Council, have proved their worth in the care and adjustment of the helpless victims of wholesale bombings.

Thus, in spite of curtailments demanded by the exigencies of wartime, the Commonwealth Fund continues its aid of scientific advance and its measures to relieve misery. Its zealous and humane efforts are an inspiration in a world in which the ideals of mercy and disinterest are challenged and must be fought for. The directors of the fund may well be proud of what has been achieved. Those who fight and those 'who only stand and stare' may be content that the torch of progress is in such hands.

## MEDICAL EPONYM

### PASTEUR TREATMENT

Louis Pasteur (1822-1895) reported his *Méthode pour prévenir la rage après morsure* [Method of preventing Rabies after Bites]" at the meeting of l'Académie des Sciences on October 26, 1885: a memorable account of its first application appears in the *Comptes rendus hebdomadaires des séances de l'Académie des sciences* (101:765-772, 1885). A portion of the translation follows:

After innumerable experiments, I have arrived at a prophylactic method that is practical and rapid whose success in dogs has already been frequent and certain enough to make me confident of its general applicability to all animals and to man himself. This method is based essentially on the following facts:

Inoculation of a rabbit by trepanation under the dura mater with rabid spinal marrow from a mad dog always transmits rabies to the animal after an average incubation period of about fifteen days.

If virus from the first rabbit is transferred by this method to a second, from this to a third and so on, there will soon be apparent a progressively increasing tendency to a diminution of the incubation period for bites in the successively inoculated rabbits.

The spinal cords of these animals are rabid through their extent, with a constant virulence.

If pieces a few centimeters in length are taken from these cords with all possible precaution regarding cleanliness, and if these are suspended in dry air, their virulence slowly disappears completely.

These facts being established, let us consider the method of rendering a dog immune to rabies, in a relatively short time.

A piece of fresh rabid cord from a rabbit killed by rabies, developed after seven days incubation, is suspended daily in one of a series of flasks, the air in which is kept dry by pieces of potash placed at the bottom of the flask. Each day, moreover, a Pravaz syringe full of sterilized bouillon, into which has been incorporated a small piece of one of these dried cords, is injected under the skin of the dog beginning with a small dose of which is a sufficient number of days

before the dry when the operation is performed so that one may be sure the cord is not virulent. On subsequent days, more recent spinal cord is used, separated by intervals of two days, until at last a very virulent cord is reached, which has been in the flask only a day or two.

The dog is now immune to rabies. He may be inoculated with rabid virus under the skin or even on the surface of the brain by trepanation, without the development of rabies.

By the application of this method, I had succeeded in obtaining 50 dogs of all ages and breeds that were immune to rabies, without having met with a single failure, when these presented themselves unexpectedly in my laboratory, on Monday, July 6 last, three persons from Alsace: Theodore Vone, a grocer of Meisengott near Schlestadt, who had been bitten in the arm on July 4 by his own dog, which had gone mad, Joseph Meister, aged nine years, also bitten on July 4, at 8 o'clock in the morning by the same dog. This child had been thrown to the ground by the dog and showed a number of bites on his hand, legs and thighs, several quite deep, that made it difficult for him even to walk.

The third person, who had not been bitten, was the mother of little Joseph Meister. Mr Vone had severe bruises on his arms, but he assured me that his shirt had not been pierced by the fangs of the dog. Since he had nothing to fear, I told him he might return to Alsace the same day, which he did. Little Meister and his mother I kept with me, however.

The death of this child seeming inevitable, I decided, not without keen and tormenting doubts as may well be supposed, to try on Joseph Meister the method that had always succeeded in my hands with dogs.

Therefore on July 6, at 8 o'clock in the evening, sixty hours after the bites on July 4, in the presence of Drs Vulprian and Grancher, the lad Meister was inoculated beneath a fold of the skin in the right hypochondrium, with a half Pravaz syringe of bouillon containing spinal cord from a rabbit dead of rabies on June 21, which had been kept since that time—that is, for 15 days—in a flask of dry air.

On subsequent days further inoculations were made, always in the hypochondria, as shown in the following table:

July 7, 9 a m	Cord of June 23 (14 day cord)
July 7, 6 p m	Cord of June 25 (12 day cord)
July 8, 9 a m	Cord of June 27 (11-day cord)
July 8, 6 p m	Cord of June 29 (9 day cord)
July 9, 11 a m	Cord of July 1 (8-day cord)
July 10, 11 a m	Cord of July 3 (7 day cord)
July 11, 11 a m	Cord of July 5 (6-day cord)
July 12 11 a m	Cord of July 7 (5 day cord)
July 13, 11 a m	Cord of July 9 (4-day cord)
July 14, 11 a m	Cord of July 11 (3-day cord)
July 15, 11 a m	Cord of July 13 (2-day cord)
July 16 11 a m	Cord of July 15 (1-day cord)

Nine rabbits were inoculated by trepanation with the various cords used so that the state of virulence of these cords might be followed.

During the last days, I had thus inoculated Joseph Meister with the most virulent rabid virus.

He had escaped, not only the rabies that his bites would have caused to develop, but that with which I had inoculated him as a control of the immunity conferred by that treatment—a rabies more virulent than that of the mad dog. From the middle of August, I viewed with confidence the future health of Joseph Meister. Today three months and three weeks after the accident his health remains all that could be wished.

R W B

## MASSACHUSETTS MEDICAL SOCIETY

## COMMITTEE ON MATERNAL WELFARE

## CASE HISTORY: FATAL MYELOGENOUS LEUKEMIA IN PREGNANCY

A twenty-eight-year-old married woman, whose past history was very incomplete, was transferred immediately to the hospital by the physician who saw her when she was six and a half months pregnant. On admission she was practically moribund. There was no history of prenatal care, but the patient had had anemia for some years. During the week before entry into the hospital, there had been increasing weakness, with multiple subcutaneous hemorrhages. Examination revealed marked pallor, a rapid, weak pulse, low blood pressure and a uterus just above the umbilicus. The urine was normal. Examination of the blood showed characteristic signs of myelogenous leukemia. There was no statement in the record about the size of the spleen. The patient, who was not in labor, died undelivered a few hours after entry. No autopsy was performed.

*Comment.* Myelogenous leukemia in itself is a rare disease, and its association with pregnancy is, of course, extremely rare. The general dictum of such a complication would obviously be to interrupt the pregnancy, because pregnancy would only aggravate the disease. That interruption would do anything except prolong life is undeniable.

Patients suffering from such blood diseases as myelogenous leukemia and pernicious anemia ordinarily do not become pregnant. Certainly, they should be advised against pregnancy.

## DEATHS

DOW — DAVID C. Dow, M.D., of Cambridge, died May 27. He was in his sixty-eighth year.

Born in Cambridge, Dr. Dow received his degree from Tufts College Medical School in 1898. He was an intern at Cambridge Hospital, where he was a member of the staff until his retirement a year ago. He was medical examiner of the first district of Middlesex County, and was a member of the Massachusetts Medical Society and the American Medical Association.

His widow, a son and a daughter survive him.

NEFF — IRWIN H. NEFF, M.D., of Detroit, died recently. He was in his seventy-fourth year.

Dr. Neff received his degree from University of Maryland School of Medicine and College of Physicians and Surgeons in 1889. He was a former superintendent of the Foxboro and Norfolk State hospitals, and was a former member of the Massachusetts Medical Society.

## WAR ACTIVITIES

## UNITED STATES ARMY

Base Hospital No. 6, recruited from the staff of the Massachusetts General Hospital, was recently ordered to active duty. The officer personnel is as follows:

*Commanding Officer:* Colonel Thomas R. Goethals.

*Surgical Service:* Lieutenant Colonel Horatio Rogers, chief.

*Medical Service:* Lieutenant Colonel Donald S. King, chief.

*Majors:* William T. S. Thorndike (registrar), Marshall K. Bartlett, Edward F. Bland, Henry H. Faxon, Trygve Gundersen, James A. Halsted, Sylvester B. Kelley, Alfred Kranes, Langdon Parsons, Robert G. Rae, Charles L. Short, Grantley W. Taylor, Jackson M. Thomas, Edward G. Thorp, John H. Talbott, James R. Lingley (chief, X-Ray Service) and James H. Townsend (chief, Section of Communicable Diseases).

*Captains:* Otto E. Aufranc, Francis H. Chaffee, Richard J. Clark, Lowrey F. Davenport, Daniel C. Dawes, Joseph H. Demers, John R. Frazee, John R. Graham, Thomas S. Hamilton, Henry M. Heyl, Daniel J. Holland, Theodore H. Ingalls, Alfred O. Ludwig, Otto D. Sahler, Spiros P. Sarris, Hermann B. F. Seyfarth, Oscar S. Staples, Somers H. Sturgis, Howard I. Suby, Eugene R. Sullivan, Garrett L. Sullivan, Howard Ulfelder, Claude E. Welch, Richard G. Whiting and John W. Zeller.

*First Lieutenants:* William E. Arnold, Robert M. Bailey, Edwin L. Canton, Calvin R. Coggins, Daniel S. Ellis, Marlow B. Harrison, Knowles B. Lawrence, Claude E. McGahey, John B. McKittrick, Sedgwick Mead, Frederick K. Poulin, Stanley W. Wyman, and William C. Burrage.

## CORRESPONDENCE

## PELLAGRA NOT A REPORTABLE DISEASE

*To the Editor:* At a meeting of the Department of Public Health on May 12, 1942, it was voted to remove pellagra from the list of reportable diseases. This action was taken because the disease has a very low prevalence in Massachusetts and the information which was being received from the reports was serving no useful purpose.

PAUL J. JAKMAUH, M.D.  
*Commissioner of Public Health*

State House  
Boston

## REPORTS OF MEETINGS

## BOSTON ORTHOPEDIC CLUB

A regular meeting of the Boston Orthopedic Club was held at the Boston Medical Library on January 19, with Dr. Otto J. Hermann presiding. The subject of the evening was "The Medical and Surgical Aspects of Gout."

The medical aspect was discussed by Dr. John Talbott, of the Massachusetts General Hospital. This disease is infrequent but not rare, and is usually undiagnosed for the first few years of its existence because its characteristic manifestations appear only in the later stages. This is in spite of the fact that the diagnosis is easily confirmed.

Gout may occur at any age from six to over seventy. There is periodic pain in multiple joints, with asymptomatic periods between attacks. At first, there are no residual manifestations, but later the interarticular changes brought about by the deposition of sodium urate appear. Although the resulting disabling symptoms may occur early in the disease, they never occur at the first attack. Any joint may be the site of attack, and the appearance of the joint in the acute stage closely resembles that in acute rheumatic fever or infection. A spread of the process may simulate cellulitis, but the skin is usually tense and cyanotic rather than red. Pitting edema and desquamation are occasionally encountered. There may be elementary or genitourinary prodromes, and an attack may occur while a patient is on accepted treatment. Sometimes a high-purine meal, recent surgery, an alcoholic bout, acute infection or trauma is the only initiating factor of an attack, and the interval between such an event and the onset may vary from a few hours to days. Each bout may last days to weeks, but there is usually a prompt response to colchicine. The interval between episodes may be as long as a decade at first, but subsequent attacks become more frequent. The association of bouts of pain with changes in weather is a real one. This has been explained by the finding that these patients have a diuresis shortly before the onset of joint symptoms, with a paradoxical gain of weight. When the barometric pressure is falling before a storm, a decrease in the insensible loss of fluid from the skin accounts for this apparent discrepancy.

The diagnosis of advanced tophaceous gout, with its tophi, increased blood uric acid content and punched-out areas of bone roentgenologically, is easily made. But it is essential to discover the early cases and thus possibly prevent some of the later sequelae by appropriate therapy. A presumptive diagnosis should be made on the history of repeated attacks of polyarthritis with no interval manifestations, a family history of gout, the excretion of urate crystals and a favorable response to colchicine therapy. The finding of a constantly elevated serum uric acid content is confirmatory evidence. The differential diagnosis involves practically all joint diseases, and any chalky secretions should be examined microscopically. For the determination of the uric acid levels, serum or plasma is preferable to whole blood, for the results are higher and the difference between normal and pathologic levels more definite. By this method, most normal patients have values below 5 mg. per 100 cc., whereas gouty patients are invariably above 6 mg. In 100 cases of gout in which 900 uric acid determinations were carried out at all stages of activity and quiescence in the past eight years, the level was over 6 mg. per 100 cc. in 99 per cent, with a variation from 5.7 to 16.0 and an average of 8.8. In 400 control determinations, the uric acid values were less than 6 mg. per 100 cc. in over 96 per cent, with an average of 4.1. Other conditions that may have a high value are renal insufficiency and leukemia. It is well known that many gouty patients have the former, and it should not be forgotten that leukemic patients may have other forms of arthritis. X-ray study is probably the least helpful in diagnosis, for the lesions are characteristic neither in place nor in kind. This aid should merely be used in suspected cases but not to rule the disease in or out of itself.

There is no known cure for gout, and residuums persist unless surgically removed. An asymptomatic period should not be accepted as a cure, but the condition may be fairly well controlled in most cases by the judicious use of appropriate therapy. The acute attack may be relieved by bed rest, high-fluid intake, soft-solid diet, a cradle over the part, sedation and colchicine. The drug

is best employed in the crystalline form in doses of 1/120 gr. every hour or two for eight to twelve times. Adequacy of dosage may be judged in the novice by the onset of nausea, vomiting and diarrhea, but the veterans know their capacity fairly well and can usually avoid these toxic manifestations. Improvement is evident in twenty-four to forty-eight hours, and repetition of a course of therapy should never be undertaken in less than two or three days. Otherwise, there will be toxic symptoms with a few doses and no relief of the gouty pains. There are no untoward reactions, sensitivities or the development of tolerance.

Treatment between attacks is almost impossible to evaluate because of the lack of a yardstick. Although the use of a low-protein and low-purine diet seems theoretically sound, its practical value is apparently exaggerated. Alcohol is not forbidden these patients despite its alleged role as an inciting factor. Cinchophen and its derivatives are banned because of the danger of liver damage and because it is not considered indispensable where colchicine is available. The use of mercury diuretics to cause an outpouring of fluid and urates was compared with a simple adenectomy in a case of lymphoma. Colchicine may be administered from every sixth day to every day, depending on the number of attacks each year, and this serves to keep the patient aware of both the disease and the drug; intensive therapy can thus be begun early in the prodromal stage. A high-fluid intake, as well as a reducing diet in obese patients, seems desirable, to relieve strain on affected joints. A high-vitamin and high-mineral diet is recommended, but no specific factor can be suggested as prophylactic.

Before discussing the surgical aspects of this disease, Dr. Robert Linton reviewed the history of gout in its relation to surgery. His cases were all in the late stages, and the procedures were often unorthodox from an orthopedic standpoint. The results were of course local and had no effect on the disease as a whole. The reasons for operation were pain, deformity and intractable ulcers. Before 1935, there were only seven operations at the Massachusetts General Hospital for the tophaceous deposits of gout, whereas between 1935 and 1941 Dr. Linton performed ninety-three operations on 11 patients. Formerly, the acute gouty joint was considered similar to that of an acute inflammation, and this was one factor in deciding against surgery. Another point, which has since been disproved, was the alleged lack of an adequate blood supply in gouty lesions. Dr. Linton has also found a decrease in the expected number of recurrences instead of the opposite. Eight patients were over fifty years of age, and 7 had had gout for over twenty years. The site of the operations—an indication of the relative prevalence of the condition—was as often in the hands as in the feet. The commonest type of growth was that involving the tissues down to but not including the bones and joints. Surprisingly, a third of the operations involved only the subcutaneous tissues and bursas. The notorious great toe was involved in only 5 per cent of all operations. The results in general were good, so far as relief of pain, decrease of deformity and increase of the function of the part were concerned. Healing was remarkably good, since sepsis occurred in only 3 per cent of cases, which were often ulcerated from the beginning. Several open lesions healed by primary union. It is necessary to institute measures to prevent the onset of acute attacks two to five days postoperatively, and colchicine in the usual doses three or more times a day for three days is sufficient. One important point of surgical technique is the use of transverse rather than longitudinal or elliptical incisions, even if multiple incisions then become necessary.

The discussion was opened by Dr. S. J. Thannhauser, of the Boston Dispensary. He stated that the polyarticular form of gout is much commoner in this country than in Europe. Italians predominate here, yet they do not have gout in Italy. They may learn new eating or other habits in this country that are conducive to the development of the condition. The difference between gout and the gouty attack was stressed by the speaker. The former is a metabolic disease in which the serum uric acid content is elevated. The latter, on the other hand, is not so clear, and may be dependent on some vasomotor instability. There may be some conditioning factor that explains why certain members of gouty families have attacks whereas others with equally high uric acid concentrations have none. Colchicine is good for the acute episode and should be so, for it has been shown that it exerts its effect on the vascular system. It has no effect on the gout or the uric acid content, although it does diminish the pain. Cinchophen, on the other hand, seems to be better for the gouty constitution and is not too dangerous.

In conclusion, Dr. Talbott stated that in his series the onset of an attack following a particular wine or meat was the exception rather than the rule. In patients studied on a metabolic ward over a period of months, no evidence of any effect of the dietary regimen could be noted. But this should not be construed to mean that patients who have such idiosyncrasies should not stay on a diet. Cinchophen has been found to lower the uric acid levels only intermittently, and nothing has yet been found to lower the values constantly and permanently.

NEW ENGLAND SOCIETY  
OF PHYSICAL MEDICINE

A meeting of the New England Society of Physical Medicine was held in the Bigelow Amphitheater of the Massachusetts General Hospital on January 21.

Dr. T. Stewart Hamilton, assistant director of the hospital, reported on one year's experience in the Physical Therapy Department. A rapid expansion in the use of the department was noted: there was an 87 per cent increase in the number of patients during the first six months. During one year, a total of 2100 patients received 21,266 treatments. The majority (56 per cent) of patients were referred by the Orthopedic Service. The percentages from the other departments were as follows: Medical, 12; Neurological, 10; Skin, 9; Fracture, 6; Surgical, 5; Eye and Ear Infirmary, 1.4; and Psychiatric, 0.6. Attention was called to a lack of understanding by many of the house officers, medical students and staff physicians of the principles of physical therapy and the value derived from its use in many conditions. An educational program has been started to remedy this. At present, a great deal of time and effort is being directed toward emergency training of physical-therapy technicians so urgently needed by army hospitals.

The practice of physical therapy at the Massachusetts General Hospital, as employed in the treatment of some familiar conditions, was described by Dr. A. L. Watkins, director of the Physical Therapy Department. A case of rheumatoid arthritis was presented to illustrate the deformities that may occur when attention is not given to proper orthopedic care and physical therapeutic measures. Prior to entry, this patient developed severe hip and knee flexion contractures and scoliosis in a marked degree. The patient was given bed rest, an adequate diet, and salicylates for control of pain, and the deformities were corrected by balanced leg traction on a Bradford frame. The muscles were strengthened, and the function of joints

was regained by supervised therapeutic exercises, at first under water in the Hubbard tub, and later by gait instruction in the walker. Attention was given to postural exercises to improve body mechanics. Local heat to joints in the form of radiant heat lamps, paraffin baths, hot wet packs and diathermy was found helpful in controlling pain, and allowed greater function of involved muscles and joints.

Cases of Bell's facial-nerve paralysis, with early and late recovery, were presented. Patients who did not show a reaction of degeneration usually recovered within three to six weeks regardless of the treatment, whereas with complete nerve degeneration, several months elapsed before beginning function was noted. In these cases, abnormal contractions of all facial muscles occurred, which is described as mass action. This phenomenon was demonstrated by electromyographic recordings. The treatment consisted of splinting, radiant heat, gentle massage, electrical muscle stimulation and graded active symmetrical exercises when possible.

In peripheral-nerve injuries, a test for quantitating the electrical excitability of degenerating and regenerating nerves by means of stimulation by measured condenser discharges was found to be of value in detecting recovery at an early date.

Copper sulfate iontophoresis was used in the treatment of facial pitting and scarring from chronic acne vulgaris, with gratifying results.

The technic of histamine iontophoresis was demonstrated. This measure was useful in producing prolonged local hyperemia for symptomatic relief of muscle pain and spasm in those conditions commonly called "periarticular rheumatism" and "fibromyositis."

Conventional long-wave diathermy has been found to be the treatment of choice in addition to immobilization for nonpurulent sclerosing tenosynovitis. When the acute inflammation has subsided, the whirlpool bath and graded active exercises are started.

The treatment of a compound fracture of the elbow, with radial-nerve involvement, was discussed. This consisted in radiant heat and gentle stroking massage, without elbow motion at first. When bony union permitted, whirlpool bath and guided active exercises of graded intensity were added. The radial-nerve paralysis was followed with electrical and functional tests, which showed spontaneous regeneration. At the end of six months, elbow motion was 80 per cent of normal, with good regeneration of the radial nerve. The patient then started work on the hand loom in the Occupational Therapy Department, to gain further supination and muscle strength and to prepare him psychologically for an early return to work.

An analysis of the types of treatments given during the past year (Table 1) revealed that simpler measures, which

TABLE 1. Analysis of Cases Treated during 1940.

TYPE OF TREATMENT	NO OF TREATMENTS	PERCENTAGE OF TOTAL
Radiant heat	9262	22.2
Massage	8661	20.9
Therapeutic exercise	16318	39.3
Hydrotherapy	2680	6.6
Ultraviolet light	1739	4.2
Diathermy	1918	4.6
Electrical stimulation and iontophoresis	926	2.2

are also suitable for home use, constituted approximately 90 per cent of the treatments. More elaborate measures involving electrotherapy constituted the remaining 10 per cent.

the new Physical Therapy and Occupational Therapy treatments were opened for inspection at the end of the month

## BOOK REVIEWS

*Eye Lining* By C E Turner, A M, Sc D, Dr P H, Elizabeth McFloss, B S, M A 8°, cloth, 432 pp., with illustrations St. Louis The C V Mosby Company, 1941 \$1.90

A textbook for the instruction of school and college students in the fundamentals of healthful living, this work based on actual classroom experience, and the material well organized and adequately presented

*Mayo Clinics A Mayo Clinic monograph* By Fred A Willis, M.D., MS in Med 8°, cloth, 276 pp., with 35 illustrations St. Louis The C V Mosby Company, 1941 \$4.00

Since there have long been the most popular form of post graduate education in American medicine because the average physician is more interested in finding out what is being practiced than what is being preached. It is through such teaching clinics that many bits of empirical clinical lore are passed along — information that, perhaps, not been dignified by inclusion in the textbooks. Dr Willis' volume has been compiled from actual discussions, which have previously appeared in the *Staff Meetings of the Mayo Clinic*. It is perhaps the first book of this type devoted exclusively to heart disease, and it makes for good reading. Examples of all the common etiologic factors of heart disease, as well as a number of unusual cases are included

*Cancer of the Face and Mouth. Diagnosis treatment and repair* By Vilray P Blair, M.D., Sherwood Moore, M.D., and Louis T Byars, M.D. 4°, cloth, 599 pp. with illustrations and 64 plates St. Louis The C V Mosby Company, 1941 \$10.00

This book is designed to help the practitioner who first meets the patient with cancer of the face and mouth. It emphasizes the need for early recognition of cancer, but places main stress on the handling of the delayed or recurrent case. Many of the patients presented might be considered incurable, but the results show that even in advanced cases one can achieve brilliant cures by the institution of proper therapy

The method of destroying cancer about the face and oral mucosa varies in different clinics. Dr Blair and his associates frequently use electrosurgical and cautery destruction. A slough is thus formed that clears away and leaves a clean base of granulation tissue. This method has the further advantage of allowing time for the detection of recurrence and its elimination before a plastic procedure is undertaken. In cancers of the tongue, local institution of radium has been used to the exclusion of surgery in the last ten years. In some cases, surgery was delayed at a later date to remove a thickening in the scar or by recurrence

Some will differ with the authors in their selection of treatment for individual cases. Apropos of this is the statement from the text, "It is not so much lack of treatment as poor selection of the kind of treatment that has most often disappointed the average recurrent case that we encounter today, but lack of conviction, temporizing methods and hurried execution. It is not delayed treatment but hasty treatment that seems to lessen the quality of our therapeutic results"

The last part of the work is devoted to a discussion of the various procedures, half the space being taken

up by the steps involved. These illustrate the cases discussed in the previous text. By this method, one is kept constantly in touch with the actual case. There is an excellent discussion of neck dissection and radiation therapy in the management of each type of lesion

Dr Blair and his group have presented a most difficult problem in a manner that will give immeasurable help to the many surgeons and practitioners throughout the country who treat patients with cancer of the face and mouth

*Wounds and Fractures A clinical guide to civil and military practice* By H Winnett Orr, M.D. 4°, cloth, 227 pp. Springfield, Illinois Charles C Thomas, 1941 \$5.00

The timing of this publication was perfect — dramatically so. In the hands of the author, the results obtained by following the technic outlined may be all that he claims. For situations in which there is such a press of work to be done that timesaving and lack of trained attendants are vital factors it is conceivable that the method may have advantages. One gets the impression that the author believes that he has introduced something new into the practice of surgery besides infrequent dressings, when he cites adequate fixation, correction of deformities, overcoming shortening and prevention of, and protection from, infection as the fundamental objects of fracture treatment

His advice to ignore the existence of shock in determining the time to institute the surgical measures needful to fulfill the above mentioned cardinal principles of fracture treatment and the assertion that a little infection in the vicinity of the fracture site may be helpful, on the ground that it might stimulate callus formation provided the wound is well drained are at least debatable. No well trained surgeon closes a wound when he has any doubt of its freedom from infection, nor does he dress it more frequently than need be. Plaster-of-Paris fixation, in skillful hands undoubtedly provides the best security for the fragments. A minimal use of hardware to secure and hold fractures in proper alignment is at times desirable, but to insert a pin indiscriminately in every case, unless it is clear that no other method will suffice, is failing to exercise good judgment, at least in the opinion of the reviewer

The chapters on the treatment of nerve injuries as a complication of fracture management and on the value of physical therapy are adequate.

The appended bibliography is confined to a list of the author's own writings on the subject of fractures

*X Ray Therapy of Chronic Arthritis* By Karl Goldhamer, M.D. With a foreword by Harold Swanberg, M.D. 8°, cloth, 131 pp., with 24 original illustrations by the author, 4 roentgenograms and 4 tables Quincy, Illinois Radiologic Review Publishing Company, 1941 \$2.00

This small monograph attempts to summarize current knowledge concerning chronic arthritis and experience with its treatment by x rays. The author, a man of wide roentgenologic experience, has presented with commendable frankness his data in the treatment of 100 patients suffering from chronic arthritis. The drawings of the roentgenologic findings are good but do not show the changes so well as good photographs of x ray films

The author believes that x ray therapy acts on chronic arthritis by stimulating hyperemia and producing improved nutrition in the joint, and also that it produces an analgesic of varying duration. He claims that better results can be expected in the early case than when the arthritis has been present a long time. The techniques are described for the various types of arthritis. The reviewer

gained the impression that the author, like many other sponsors of measures of definite value, is somewhat over-enthusiastic.

*Endocrinology: The glands and their functions.* By R. G. Hoskins, Ph.D., M.D. 8°, cloth, 388 pp., with 14 illustrations. New York: W. W. Norton and Company, Incorporated, 1941. \$4.00.

It is always difficult to write a book on a scientific subject that will be of value both to the general reader and to the student of the subject. Essentially, this is what the author has undertaken, this work being based on an earlier book, *The Tides of Life*, which appeared in 1933. As Dr. Hoskins states in the preface, "The material has been brought up to date and amplified with an eye particularly to the needs of biologists, psychologists, premedical students and those physicians who desire a not-too-technical introduction to the science of the hormones. I have also tried, however, to keep for the most part within the comprehension of the intelligent general reader." The reviewer believes that there are few general readers with sufficient biologic and medical knowledge to follow the author's discussion with much understanding. For the other group mentioned, it should be very useful.

The author has dedicated the book to "W. B. C." (Walter B. Cannon). After a brief introduction on hormones as chemical regulators, a chapter is devoted to each endocrine gland. There is a chapter on general aspects of endocrinology, such as its relations to the nervous system, the interrelations among the endocrine glands, racial characteristics, endocrine diagnosis and therapy, and endocrine factors in personality. Finally, a short discussion of "Endocrinology of the Future" enumerates some of the unsolved problems of the present that it is hoped will eventually be solved.

The material has been well chosen and clearly presented. Some few statements seem open to question. For example, on page 43, it is stated, "Despite its profound effects in adrenal deficiency, an excess of cortin apparently does no harm." Again, on page 329, the author implies that diabetes is generally treated with a high-fat, minimum carbohydrate diet. But on the whole, the book is most carefully written. There are references at the end of some of the chapters, and a brief general list of sources at the end of the book. A good index is included.

*Epilepsy and Cerebral Localization: A Study of the mechanism, treatment and prevention of epileptic seizures.* By Wilder Penfield, M.D., D.Sc. (Oxon., Princeton) and Theodore C. Erickson, M.Sc., M.D., with a chapter by Herbert H. Jasper and one by M. R. Harrower-Erickson. 4°, cloth, 623 pp., with 163 illustrations and 17 tables. Springfield, Illinois: Charles C Thomas, 1941. \$8.00.

A complete treatise on epilepsy, particularly one that would reflect the vast amount of research on this disease, has long been needed by the medical profession. In recent years, six general books have been published: one in French by Crouzon (1929), one in German by Frisch (1937) and four in English by Lennox and Cobb (1928), Muskehs (1928), Jackson (1931) and the extensive and able reports by many investigators issued by the Association for Research in Nervous and Mental Diseases (1931). All these books are at least ten years old, at a time when more knowledge of the treatment of epilepsy

has been added to medicine than in any other comparable decade.

It is of interest, moreover, that this book should have come from a neurosurgical clinic, the first to do so, which reflects the importance of surgery in the treatment of the convulsive state. Medical treatment is by no means neglected in this volume, but, as might be expected, the tone is set by surgery: experimental, investigative and therapeutic. Chapters are added on electroencephalography and on psychologic studies of epileptic patients.

The chief sections deal with the history of the disease, seizure patterns, — of which the senior author has been the leading investigator, — cerebral localization of these patterns, epileptogenic lesions, such as scars and tumors, the radical treatment of such lesions, diffuse diseases of the brain with cryptogenic epilepsy, and acute head injury. Clearly presented and carefully considered, the material is largely factual and reports, without too wide a generalization, what the authors have seen and reasoned about in their large clinic. This is therefore a personal book, a report of stewardship, largely by Dr. Penfield, who, in training and habit of thought, is eminently fitted to present his findings. That everyone will agree with the amount of surgical therapeutics he uses or with the value of some of his work as a practical form of relief is not to be expected. What is acceptable by the whole profession is a careful study of the epileptic constitution, in which Penfield and his colleagues have had a leading part.

For all who wish to be abreast of the times in the study and treatment of one of the most widespread and disabling of diseases, long an outcast from research, this fine product, in a fitting format, is recommended.

*An Introduction to Medical Science.* By William Boyd, M.D., M.R.C.P. (Edin.), F.R.C.P. (Lond.), F.R.S. (Canada). Second edition, thoroughly revised. 8°, cloth, 358 pp., with 124 illustrations. Philadelphia: Lea and Febiger, 1941. \$3.50.

Someone defined the introduction to a book as that part written last, printed first and seldom read. Although such a statement may be true of some books that are written to introduce the reader to a particular art or science, it is not so with this volume, which attempts briefly to encompass medical science and yet contains numerous facts accurately and delightfully recorded. In the second chapter, the author gives a bird's-eye view of the evolution of medical science. In eight pages, he covers the ground from the magic man or the witch man of primitive times to the magic bullets — chemotherapy — of the present day. As on an airplane trip, one visualizes the high peaks on the long journey. This is true of every chapter, and many facts are recorded in an authoritative and attractive manner. Dr. Boyd handles the microscope and the pen with equal dexterity. The following sentence is a striking example: "The gall-bladder has the same nerve supply as the stomach, so that the symptoms of gall-bladder disease are usually referred to the stomach, which seems to cry aloud in sympathy."

This is a book primarily written for nurses. Any nurse who can master all the facts presented will certainly serve in her profession more intelligently. The volume is highly recommended, for it is the product of a person who knows the facts and knows how to present them.

(Notices on page x)

# The New England Journal of Medicine

Copyright 1947 by the Massachusetts Medical Society

VOLUME 226

JUNE 11, 1942

NUMBER 24

## CHEST PAIN IN PATIENTS WITH MITRAL STENOSIS, WITH PARTICULAR REFERENCE TO SO-CALLED "HYPERCYANOTIC ANGINA"\*

ALEXANDER M. BLUMFELD, JR., M.D.,† AND LAURENCE B. ELLIS, M.D.‡

BOSTON

PATIENTS with mitral stenosis often complain of chest pain. Pain also frequently occurs from causes unrelated to the heart, but such pain is not discussed in this paper. There are four main varieties of chest pain especially associated with mitral stenosis: that of cardiac neurosis, that of active rheumatic carditis; angina pectoris, and so-called "hypercyanotic angina." In none is the pain directly produced by the stenosed mitral valve. In addition, patients with mitral stenosis are prone to develop pulmonary infarction and may have repeated episodes. Pain may be present either as pleural pain of an associated pleuritis or as substernal distress, especially with massive pulmonary infarctions or emboli.

### PAIN OF CARDIAC NEUROSIS

Without doubt, the type of chest pain that patients with mitral stenosis most commonly complain of is that of cardiac neurosis, such pain, for which no organic cause can be demonstrated, is largely psychogenic in origin and usually dependent on an anxiety state. It is very variable, ranging from aching soreness or pins and needles sensation, to sharp, stabbing or lancinating, and is usually felt in the apical region, occasionally all over the precordium and even sometimes in the chest and down the arms. It has no constant relation to exertion and frequently persists for hours or days. The pain is often attended by precordial hyperesthesia. Breathlessness, which in reality consists in sighing or a sense of inability to get enough

air into the lungs, is a common complaint. There may or may not be associated manifestations of neurocirculatory asthenia such as tachycardia, palpitation, cyanotic cold extremities, fatigability and poor response to effort. Part of the usual diagnosis of such functional pain is the absence of evidence of organic heart disease, but not uncommonly patients with unquestionable organic heart disease, including mitral stenosis, have unmistakable functional pain. The association is obviously explained by natural anxiety when patients know of their heart disease and its dangers. Does marked enlargement of the heart, such as some patients with mitral stenosis have, in itself cause precordial pain? Certainly, patients with very large hearts beating forcibly against the chest wall are likelier to have heart consciousness than normal persons, but such a sensation rarely, if ever, reaches the degree of true pain in the absence of a neurotic or anxiety factor. The following is a typical example of a patient with the functional type of pain.

CASE 15. The patient a 42 year old woman, who had rheumatic fever in her youth, but following this led a normal life, was married and had two children. Following the birth of the second child, she did not regain her strength, but suffered from breathlessness at her accustomed tasks and complained of a great sense of fatigue and of sleeplessness and precordial pain. She was seen in consultation at this time by an able cardiologist, who found mitral stenosis and apparently interpreted this as the cause of her complaints and stressed merely the necessity of a cautious regime on her and her husband. For 20 years the patient was up only a few hours a day, rarely went out, and was almost constantly conscious of her heart. Distressing precordial pain was the most prominent of her many symptoms. She never developed congestive failure. Suddenly, after 20 years of cardiac neurosis and no heart failure, without warning, she developed a right hemiplegia, probably from an embolus. She recovered partially from the paralysis, but her personality clearly changed. She became cheerful, fearless and free from complaints. There

\*Read at a meeting of the New England Heart Association, Boston City Hospital, March 12, 1940.  
†From the Thorndike Memorial Laboratory, the Second and Fourth (Harvard) Medical Services, Boston City Hospital, and the Department of Medicine, Harvard Medical School.

‡Formerly assistant in medicine, Harvard Medical School, assistant in medicine, Boston City Hospital, and research fellow, Thorndike Memorial Laboratory.

§Now in medicine, Harvard Medical School, assistant visiting physician, Boston City Hospital, assistant physician, Thorndike Memorial Laboratory.

††This case has previously been cited by Ellis and Blumfeld.



was no more mention of consciousness of the heart and heart pain. The patient struggled about the house doing more work than she had done at any time for the previous 20 years, and remained up all day. This state continued until she was lost sight of several years later.

The pain in this patient was of the severe type described above. For twenty years, she was disabled by a functional state, aggravated undoubtedly by the misinterpretation of symptoms by the cardiologist who first saw her. The spontaneous relief of the neurotic symptoms with the onset of an organic disability, the hemiplegia, is of interest and has been discussed elsewhere.<sup>1</sup>

#### PAIN OF ACTIVE RHEUMATIC CARDITIS

It is well known that pain in the chest may accompany active rheumatic carditis. This symptom has been thoroughly discussed by Swift and Hitchcock.<sup>2</sup> This type of pain is said to be commonest in acute recurrences of rheumatic fever, and accordingly should sometimes appear in patients with mitral stenosis. The following case illustrates most of the typical features of this type of pain.

CASE 2. A. M., a 37-year-old woman, had had acute rheumatic fever at the age of 14, and had been known to have mitral stenosis and auricular fibrillation for several years. She entered the Boston City Hospital because of persistent, dull, heavy, aching pain, located in the mid-sternal region and nonradiating. In association with this was hyperesthesia of the precordial region of sufficient degree to make cardiac percussion uncomfortable to the patient. She had, on admission, in addition to the physical signs of her valvular lesion, mild migratory joint pains, a slight fever, leukocytosis and elevated sedimentation rate. As these latter findings disappeared so did the patient's precordial pain and hyperesthesia, and she recovered uneventfully.

The pain in this case was consistent with cardiac neurosis, but there were no other neurotic symptoms, and the occurrence and subsidence of the pain in conjunction with the onset and disappearance of signs of rheumatic infection indicate its relation to active carditis. Active rheumatic carditis may be accompanied by pericarditis, and if the diaphragmatic or a certain part of the pleural pericardium is involved, there may be pain in the precordium, the root of the neck or upper abdomen.

#### ANGINA PECTORIS

It has long been recognized that angina pectoris is rarely associated with mitral stenosis. White<sup>3</sup> found mitral stenosis in but 2 of 500 cases of angina. Hamilton and Thomson<sup>4</sup> found but one patient with an unmistakable story of effort limited by angina pectoris among many hundred young women of child-bearing age with mitral stenosis. Although evidence exists that rheumatic fever may

produce or hasten organic disease of the coronary arteries,<sup>5</sup> the rarity of angina pectoris except in patients in the older age group and usually with other clinical evidence of arteriosclerosis makes it probable that when this symptom does occur it is usually due to a superimposed coronary atherosclerosis and does not differ essentially from angina pectoris occurring in patients without valvular heart disease. Blackford<sup>6</sup> has recently reported 2 cases of angina in patients with mitral stenosis who had normal coronary arteries. One of these cases presented features suggesting that it falls into the group of "hypercyanotic angina," discussed below. Uncommon as angina pectoris is in association with mitral stenosis, acute myocardial infarction is even rarer. White<sup>7</sup> did not encounter a single case of mitral stenosis in a series of 200 cases of myocardial infarction. The characteristics of the pain of angina pectoris are too well known to need description. The following is an example of a case of angina pectoris and mitral stenosis.

CASE 3. P. R., a 50-year-old man, entered the hospital in acute congestive failure and stated that for the previous 5 weeks he had had increasingly frequent attacks of severe precordial pain and tightness, precipitated by even mild exertion and radiating down the left arm in the form of "numbness" or a "twisting" pain. The patient had a clear history of several attacks of rheumatic fever in childhood and typical physical and x-ray findings of mitral stenosis. The patient's failure responded to the usual treatment, but when allowed up and about he had frequent return of his precordial pain on effort.

#### HYPERCYANOTIC ANGINA

Perhaps the most dramatic precordial pain occurring in patients with mitral stenosis is the unusual type of paroxysmal precordial or substernal pain, called "hypercyanotic angina" by some authors. This pain, since it occurs principally in cases of severe mitral stenosis, may well bear some direct relation to the valvular lesion. The pain is severe and may be excruciating, lasting hours or even days in extreme cases. It is clinically indistinguishable from the pain of an acute myocardial infarction but is associated with none of the electrocardiographic changes, fever and leukocytosis that accompany the latter, and at post-mortem examination there is no evidence of infarction. The following cases are presented as extreme examples of this type.

CASE 4. E. R., a 33-year-old woman, gave a history of rheumatic fever in young adult life, and signs of progressively diminished cardiac reserve for 6 years. For 2½ years, she had suffered increasingly frequent and severe attacks of dyspnea, orthopnea, cyanosis and very severe precordial pain, burning in character and radiating to the left side and back of the chest, with a sensation of warmth in the left arm. The first attack was of 5 days' duration and was repeated in varying degrees of severity during

the months prior to entry. Between attacks, the patient was quite well except for mild exertional dyspnea and the occurrence of five hemoptyses.

On entry, the patient seemed acutely ill, complaining of severe pain, with marked cyanosis, moderate orthopnea and some venous distention. There was slight congestion of the right lung base. The heart was enlarged, with signs of mitral stenosis, and the liver was enlarged and slightly tender. The blood pressure was 68/30, and rose to a normal level following the attack. The patient responded to oxygen and sedation, and the patient was then well except for low grade fever and leukocytosis. Attacks of pain recurred several times during the hospital stay, always with severe cyanosis, pulmonary edema and collapse, and oxygen seemed always to be the deciding factor in their relief. Electrocardiograms showed T-wave abnormalities affecting digitalis therapy, and they showed no change during the entire course except for a shift from sinus rhythm to auricular fibrillation. The patient died during the 12th hospital week in another severe attack of preterminal pain.

Post-mortem examination revealed a markedly stenosed, thickened and fixed "button-hole" mitral valve, a normal size of coronary arteries, which were patent and showed no sclerosis, and a myocardium that was hypertrophic in the region of the right ventricle but otherwise unremarkable. The pulmonary changes in this case were very marked and have been reported in detail by Parker and Cass<sup>8</sup> in their study of pulmonary vascular changes secondary to mitral stenosis. These changes consisted in general of marked capillary dilatation, with a tendency to aneurysmal bulging into the alveolar lumens; thickening of the capillary basement membrane, a tendency to intimal fibrosis in the alveolar walls and in many areas the appearance of a cuboidal type of epithelium in the lumen. The larger arterial vessels showed a proliferative arteritis.

Case 5. J. P., a 65-year-old woman who had had acute rheumatic fever in childhood, entered the hospital because of several weeks of intermittent severe "pressure-pain" in the left chest, with radiation to the left arm, which had been almost constant for the 2 weeks prior to admission. It was unrelated to activity. On entry, the patient showed orthopnea, cyanosis and extreme prostration. The heart was totally irregular, and there was a rough apical systolic murmur. There were slight pulmonary congestion and minimal peripheral edema. The blood pressure was 110/50. The patient continued to be apparently in extremis throughout the entire 1st hospital week, after which she improved slightly but had frequent recurrences of pain, and she was discharged after 4 months.

During the succeeding year, the patient entered three or four times for similar severe episodes, the last admission being 5 weeks of apparently continuous pain and prostration. At all these admissions, there was slight objective evidence of pulmonary congestion and none of peripheral edema. At the last entry, physical and electrocardiographic findings were still those of the first admission. The patient died on the 32nd hospital day following her severe attack.

Autopsy showed a 300 gm. heart, the coronary vessels having normal patency but mild atheroma, and the myocardium showed only microscopic perivascular fibrosis. The mitral valve was thickened and stenosed, and the coronary vessels showed changes similar to those in Case 4 although somewhat less marked.

Case 6. M. Y. entered the hospital six times between the ages of 48 and 58. She gave a history of two attacks

of acute rheumatic fever in early adult life, and for 18 months prior to entry she had had bouts of severe precordial pain radiating down the left arm and accompanied by cyanosis and dyspnea. On each entry, the story was striking, with severe and prolonged precordial pain and cyanosis—lasting several hours at a time and not related to exertion. There was evidence of slight persistent pulmonary congestion, but no peripheral edema, throughout each entry. Attacks recurred at frequent intervals, and were best relieved on those occasions when the patient received oxygen therapy in the hospital. During one attack, the blood pressure rose from 150/100 to 200/130, returning subsequently to its previous level; in another attack, the blood pressure fell. The patient had chronic auricular fibrillation throughout her course, and marked signs of mitral valvular disease. The final hospital admission followed a month of continuous pain and congestive heart failure and ended in death. The only electrocardiographic change from the findings at the first admission until death was a gradual shift of the axis toward the right. Unfortunately, permission for post-mortem examination was denied.

## DISCUSSION

In brief, the picture presented by the last 3 cases and by a few similar ones in the literature is as follows. The pain is severe, squeezing or grinding, located in the precordium or beneath the sternum, radiating to the left shoulder and arm, bearing no clear relation to exertion, emotion or stress, and occurring in paroxysms that may last for hours or days. In addition, there are usually dyspnea, orthopnea and a severe degree of cyanosis during the attacks, and in some cases marked circulatory collapse. Peripheral venous congestion may or may not be present. Although our patients all had some congestion of the lungs at the time of the attacks, the relation of the pain to heart failure is by no means constant. The picture that these patients present is often unlike the usual manifestations of heart failure. Their cyanosis may be extreme, and their dyspnea and orthopnea well marked at a time when the signs of pulmonary congestion are surprisingly few. Roentgenograms of the lung fields are likelier to show markedly increased hilar markings and shadows of enlarged pulmonary vessels fanning out from the hilum than the usual basal congestion.

There is not the fever, leukocytosis or electrocardiographic pattern of an acute myocardial infarction, and the changes in blood pressure are irregular and in no way characteristic. Oxygen relieves the pain much more effectively than vasodilator drugs. Post-mortem examination shows a high degree of mitral stenosis, with secondary myocardial hypertrophy and pulmonary vascular changes.

This symptom complex, which is by no means new, is seen occasionally in most large clinics. It is, however, confusing and often leads, as in all 3 of our cases, to a mistaken diagnosis of myocardial

infarction. Striking as it is, it has received relatively little attention in the medical literature and has escaped mention in most of the standard texts. It is probable that mild grades of this syndrome occurring in patients with marked mitral stenosis are not so uncommon as observers have thought.

The first definite mention of chest pain as a feature of mitral stenosis is contained in an article by Nothnagel,<sup>9</sup> who, in 1891, presented statistics concerning the frequency of occurrence of pain in all types of valvular heart disease. The aortic lesions, of course, led the field, but it is of interest that he recorded pain in 18 per cent of his cases of mitral stenosis. He further reported a case of severe prolonged precordial pain in a thirty-six-year-old woman whose story is very similar to that in Cases 4, 5 and 6.

Since the turn of the century, there have been a few scattered articles dealing with pain of this type, further describing and sometimes attempting to explain it. Vaquez and Giroux,<sup>10</sup> in 1908, described the clinical picture of *angina pulmonaire hypercyanotique*, which they considered a consequence of pulmonary vascular abnormalities. Posselt,<sup>11</sup> in the same year, mentioned *Dyspragia intermittens angiosclerotica pulmonalis*, apparently the same syndrome, as one of the criteria to be used for the clinical diagnosis of pulmonary arteriosclerosis, and suggested that the pain might be produced by distention of the pulmonary arteries caused by pulmonary arteriolar spasm. In 1911, Frugoni<sup>12</sup> contrasted the *dolor pallidus* of ordinary effort angina with the *dolor caeruleus* in patients with sclerosis of the pulmonary vascular system. He believed that the pain had a distinctive type of radiation, differing from that of ordinary angina, from the precordium deep into the chest, an opinion that was echoed by Engelen<sup>13</sup> in 1923. Arrillaga,<sup>14</sup> in discussing Ayerza's syndrome, comments on the occasional occurrence of pain of the type described by Posselt.

The writings of Brenner<sup>15</sup> on the pathology of the pulmonary circulation contain some further mention of hypercyanotic angina occurring in patients with secondary pulmonary arteriosclerosis. Of particular interest, however, is the case that he cited of an eleven-year-old boy who had primary pulmonary arteriosclerosis of sufficient degree to cause marked right ventricular hypertrophy. The description of the pain is identical with that in our cases. This is, interestingly enough, the only case of this phenomenon in the literature occurring in a male. Brenner suggests that the pain is the result of myocardial anoxia, which is caused by the severe anoxemia.

Brill and Krygier,<sup>16</sup> in a recent review of primary pulmonary vascular sclerosis, commented on the oc-

currence of chest pain in 4 of the 20 cases they assembled from the literature, including 1 reported by themselves, and considered that the pain was probably due to acute coronary insufficiency consequent to a diminished volume of blood delivered to the left ventricle through an obstructed pulmonary circulation.

In the foregoing discussion, attention has been devoted primarily to disorders of the pulmonary circulation. Although in some cases these disorders are associated with mitral stenosis, they frequently occur in patients suffering from chronic pulmonary disease or even primary pulmonary vascular disease.

There has been some comment in the literature specifically of the association of pain of this type and mitral stenosis. Parker and Weiss<sup>8</sup> mentioned pain and cyanosis prominently among the symptoms of their cases of mitral stenosis with severe secondary pulmonary changes, and commented on their absence in the control cases with a normal pulmonary circulation. They made the suggestion that the cyanosis is due to a number of factors. The alveolar capillaries are so dilated as to allow simultaneous passage of several columns of red cells instead of the normal one, with consequent inefficient oxygenation, and the structural changes that they describe are such as to increase greatly the thickness of the membrane through which the gaseous exchange must occur.

Some authors have attributed the pain to strictly intracardiac explanations of conditions. Sternberg,<sup>17</sup> in reporting the autopsy findings in a twenty-six-year-old woman with mitral stenosis who had severe precordial pain for five days preceding death, noted that the coronary arteries were unusually thin and collapsible, and suggested that the terminal precordial pain was the result of compression of the left coronary artery in its course between the left auricle and the pulmonary conus, which were distended as a consequence of the mitral stenosis. Hochrein<sup>18</sup> later took issue with this theory, stating that in his experience pain had been independent of the degree of decompensation. He offered an alternative explanation based on the post-mortem findings in 1 of 4 cases that he reported. Using a special technic, he demonstrated that the left coronary orifice was pulled down and distorted as a result of the contraction of a scarred mitral valve and its shortened chordae tendineae. This, he suggested, had sufficiently impaired the coronary flow to explain the pain.

It seems reasonable to assume, from the character and location of the pain, that it arises from anoxia of the myocardium. The relief of pain by oxygen that occurred in our patients certainly suggests that anoxia is the cause and that general de-

saturation of the blood with oxygen is an important factor. In addition, there is probably a decrease in the amount of blood reaching the left side of the heart through the impaired pulmonary vascular bed, and hence the left ventricular output is diminished. This in turn causes impairment of coronary blood flow, which thus further enhances the myocardial anoxia. It is likely that an abnormal heart is also a necessary part of the picture in addition to an abnormal pulmonary vascular system producing anoxemia and diminished blood flow. Although disease of the coronary arteries may be present, it is unnecessary in the production of the clinical syndrome, and, in view of the cases of primary and secondary pulmonary vascular disease cited above, mitral valvular disease is also not an essential feature. The common denominator of all cases is myocardial hypertrophy of the right ventricle.

The pain in character and duration is similar to that occasionally seen in patients with impaired coronary circulation or myocardial hypertrophy, or both, who develop coronary insufficiency as the result of paroxysmal tachycardia. In our cases, tachycardia of any degree did not occur.

In severe mitral disease, several factors could promote deficiency of the myocardial oxygen supply. In the first place, the increased load of work thrown on part of the myocardium by the damaged valve creates an abnormally high need for oxygen, and hypertrophy of the overworked portion of the myocardium, which in itself constitutes an unfavorable situation from the nutritional standpoint, makes this increased need the more difficult to meet. When one adds to this the anoxemia that is present, and an impaired coronary blood flow resulting from a cardiac output diminished by the obstruction in the pulmonary circulation, as well as the mechanical narrowing of the mitral orifice, the presence of pain is not surprising.

It is to be recognized that the foregoing explanation does not answer all the questions posed by this syndrome. One such question is the lack of definite correlation between the pain and exertion. One must assume that the capacity of these patients for physical exertion was sharply limited by dyspnea before pain occurred. When they became well compensated, oxygenation was sufficient to allow for moderate effort without pain. The lack of electrocardiographic change during the attacks is of interest, since it is well known that electrocardiographic abnormalities may develop during coronary insufficiency occurring in angina pectoris or from other causes. However, such alterations

in the electrocardiogram are by no means invariable in angina pectoris, and it is quite possible that further electrocardiographic studies on patients with hypercyanotic angina will reveal on occasion alterations consistent with coronary insufficiency. Furthermore, since the myocardial anoxia is general and not focal, striking electrocardiographic abnormalities are less likely to occur.

The one sided sex distribution of the reported cases is puzzling, but may diminish or disappear as more cases come to light.

### SUMMARY AND CONCLUSIONS

Four types of chest pain occurring in patients with mitral stenosis are described, and cases illustrating each type are reported. The types of pain are that of cardiac neurosis; that of acute rheumatic carditis, angina pectoris, and so called "hypercyanotic angina."

The literature bearing on hypercyanotic angina is discussed.

It is suggested that this type of pain is due to anoxia in a hypertrophic and overworked myocardium. This anoxia is explained as the combined result of severe organic changes in the pulmonary vessels, with pulmonary congestion and arterial anoxemia, in addition to reduced blood flow to the left ventricle and hence to the coronary arteries.

### REFERENCES

- 1 Ellis L B and Hamilton B E. Pain in the region of the heart. *Am Clin North America* 19:533 1945 1936
- 2 Swift H F and Hilditch C H. Cardiac pain in rheumatic fever. *Tr J Am Phys* 42:278 284 1927
- 3 White F D. The clinical significance of cardiac pain. In *Diseases of the Coronary Arteries and Cardiac Pain*. Edited by R L Levy. 445 pp. New York: The Macmillan Company 1936. P 269
- 4 Hamilton B E and Thomson K J. *The Heart in Pregnancy and the Childbearing Age*. 402 pp. Boston: Little Brown and Company 1941. P 264
- 5 Karsner H T and Bayless F. Coronary arteries in rheumatic fever. *Am Heart J* 9:557 585 1934
- 6 Blackford L M. Mitral stenosis as a cause of angina pectoris: report of two cases with necropsy. *Br Heart J* 20:492-497 1940
- 7 White F D and Weiss S. The nature and significance of the structural changes in the lungs in mitral stenosis. *Am J Pathol* 12:573 598 1936
- 8 Voeltzgen H. Schmerzhaftes Empfinden bei Herzkrankungen. *Zeitschr f klin Med* 19:209 214 1891
- 9 Vaquez and Groin. Artérios-lerose, l'entassement de l'artère pulmonaire avec atherome: rôle de l'hypertension dans la genèse de l'artériosclérose. *Bull et Mem Soc med d'hop de Paris* 26:183 189 1903
- 10 Pavesi A. Die klinische Diagnose der Pulmonalarteriosklerose. *Verh fte Mittellung. Marchen med Wchnsch* 55:1625 1679 1908
- 12 Frugoni. Sintomatologia generale delle arteri sclerose viscerali. *Med*
- 13 Engelen P. Sklerosen im Gefäß der Arteria pulmonalis. *Deutsche med Wchnsch* 49:1015 1973
- 14 Arrivabetti F C. Sclerose de l'artère pulmonaire secondaire à certains états pulmonaires chroniques (cardiaques, etc.). *Arch et mal de cœur* 6:518 579 1913
- 15 Prenter O. Pathology of the vessels of the pulmonary circulation. Part III. Secondary pulmonary vascular sclerosis. *Arch Int Med* 56:271 282 1935
- 16 Brill E C and Krayer J J. Primary pulmonary vascular sclerosis. *Arch Int Med* 68:260 57 1941
- 17 Sternberg M. Senkardie bei Mitralleiden. *Zeitschr f klin Med* 97:110 122 1973
- 18 Hochheim M. Ueber Angina pectoris bei Mitralstenose. *Deutsche Arch f klin Med* 18:195 204 1940

## THE SYNDROME OF CERVICAL RIB WITH SUBCLAVIAN ARTERIAL THROMBOSIS AND HEMIPLEGIA DUE TO CEREBRAL EMBOLISM\*

### Report of a Case

SIBLEY W. HOOBLER, M.D.†

BOSTON

IT IS not generally appreciated that thrombosis of the subclavian artery may in rare cases be the source of cerebral embolism. Symonds,<sup>1</sup> in 1927, reported 2 cases in which absent arterial pulsations in the right arm, apparently resulting from cervical ribs, had been complicated by the sudden development of left hemiplegia. His explanation was that "... pressure of the cervical rib upon the right subclavian artery led to thrombosis, that the thrombus extended backwards to the point of junction with the right common carotid, and a portion of it becoming broken off formed an embolus in one of the terminal branches of the right middle cerebral artery."

The fatal outcome in such a case was described one year later by Yates and Guest.<sup>2</sup> Their patient had complained of progressive pain and weakness of the right hand and forearm for some months. An absent arterial pulsation in the right upper extremity and an ununited fracture of the right clavicle were found. Before treatment could be instituted, the patient was taken suddenly ill with pain in the head and throat, loss of vision, unconsciousness, left hemiplegia progressing to quadriplegia, coma and death on the seventh day. Autopsy revealed an old ununited fracture of the right clavicle, with backward and downward displacement toward the right subclavian artery. This vessel was filled with an organized and very adherent thrombus, which extended to within 1.0 cm. of its junction with the right common carotid artery. A well-marked embolus was found at the division of the basilar artery into its terminal branches. The authors suggested that in this case the embolism had occurred through the escape of a fragment of the thrombus up the right vertebral artery.

More recently, Smith<sup>3</sup> has reported a similar case, in which the autopsy findings conformed even more closely to Symonds's original explanation of the course of the embolism. The patient, a twenty-two-year-old seaman, suddenly developed a left hemiplegia. He had occasionally complained of a mild, tingling sensation in the right arm and hand that had never incapacitated him. At the

time of the cerebral accident, no pulse could be obtained anywhere in the right upper extremity. Shortly thereafter, the patient lapsed into coma and died. Autopsy revealed a thrombosis of the right axillary and right subclavian arteries, apparently originating in a small, sacculated congenital aneurysm attached to the right axillary artery. The thrombus extended as far as the origin of the right common carotid artery, and a large embolus was found occluding the right internal carotid artery where it enters the carotid canal.

In a brief review of the literature, only one other case could be found that may represent the combination of events first recognized by Symonds. This was reported by Gould<sup>4</sup> in 1884. Although the author apparently did not recognize the pathogenesis of the symptoms, calling it a case of "obliterative arteritis," his description is very clear, and the clinical course similar to the case to be reported. It may be summarized as follows:

C. B., age 19, a laborer in a brickfield on the Isle of Wight, was admitted to the London Temperance Hospital on October 13, 1883. At the end of April, 1883, he noticed the fingers of his right hand getting "dark" in color. The hand seemed weak; when at work it quickly became cold and then there was a "sickening pain" in it.

State on admission: the limb below the elbow was distinctly colder than the opposite one. Just above the elbow all pulsation ceased. The radial artery was a prominent hard, pulseless cord. A great prominence of the right subclavian artery above the clavicle was noted; it projected under the skin as a tense pulsating cylinder which was bulging forward even beyond the level of the clavicle. Springing from each side of the lower two cervical vertebrae was found a hard, immovable, irregular mass apparently bony. When the subclavian artery was pressed against the mass in a particular direction, a thrill was produced in it.

In a second communication, three years later the author<sup>5</sup> stated:

This patient was shown to the Society two years ago. Since then he remained at work as a labourer until six months ago, when he was attacked with numbness in the right arm and forearm, accompanied by severe headache. . . . Four months ago he suddenly lost power in the left arm, and the same evening he became unconscious. Next day he spoke and moved his arm. He noticed the pulsation of his right subclavian artery until four months ago, not since.

\*From the Medical Clinic, Peter Bent Brigham Hospital, and the Department of Medicine, Harvard Medical School.

†Assistant resident in medicine, Peter Bent Brigham Hospital.

The right forearm is distinctly colder than the left. The axillary and the third part of the subclavian artery can be plainly felt as a hard pulseless cord.

The sixth reported case of this unusual complication of subclavian arterial thrombosis follows.

### CASE REPORT

D L, a 38-year old carpenter, was admitted to the Medical Service of the Peter Bent Brigham Hospital on February 3, 1941, with a history of weakness and inability to walk.

Two hours before admission, the patient had noticed sudden weakness of the left hand so that he had dropped his lunchbox twice, felt weak in the knees and had had to be assisted in walking to his place of employment. Because no improvement occurred after 2 hours, he was sent into the hospital.

Two years previously, he had come to the Out Door Department complaining of numbness, tingling pain and weakness in the right hand of 6 weeks duration. Examination had revealed weak right radial normal brachial and increased right subclavian arterial pulsations. Weakness and some atrophy of the muscles of the right hand had been noticed, without sensory impairment or decreased skin temperature. X-ray study revealed bilateral cervical ribs. At operation, it was noted that the subclavian artery lay higher than usual, presented a normal caliber and amplitude of pulsation, and did not appear compressed over the rib. Since the brachial plexus also did not appear unduly stretched, it was decided to cut the scalenus anticus muscle and not attempt resection of the rib. Complete symptomatic relief and considerable increase in the amplitude of the right radial pulsation had followed the operation until 6 months before admission, when the patient again complained of mild weakness and occasional paresthesias of the right hand and a decreased right radial pulse. These symptoms had been exacerbated in the 2 weeks prior to admission and he had in addition noted recurrent pains about the right shoulder and supraclavicular fossa.

The patient had enjoyed excellent health except for a brief attack of neuritis involving both upper arms 16 years before, and an episode of right facial weakness diagnosed as Bell's palsy 12 years prior to this admission.

At the time he was admitted to the ward, neurologic examination revealed a left hemiparesis and weakness of the left lower facial musculature. The deep tendon reflexes were increased on the left. Except for the facial weakness, the cranial nerves were intact. The pupils were equal and reacted well. There was no dysarthria or aphasia. Sensation was nowhere impaired. The Babinski and Kernig signs were absent.

The right radial and brachial pulses could not be detected and the axillary pulse was greatly diminished. However, pulsation in the right subclavian artery was increased. The blood pressure on the right could not be obtained, but in the left arm it was 120/70, and on this side arterial pulsation was normal. On palpation, no difference in the skin temperature of the two upper extremities could be noted, and there was no evidence of cyanosis or muscular weakness on the right side.

The heart was not enlarged to percussion. The rate was regular, 78 beats per minute, and no murmurs were heard. The remainder of the physical examination was likewise negative.

Laboratory data, which included routine blood, urine and stool examinations, lumbar puncture and skull films, showed no essential deviations from the normal. The Hinton and Wassermann reactions on the blood and spinal fluid were negative.

Following hospitalization, improvement in the neurologic findings was striking. The day following admission only moderately increased tendon reflexes on the left and a positive Barre sign bore witness to the patient's previous disability.

Five days after entry however he began to complain of pain about the right shoulder and numbness of the right hand. Overnight, the right subclavian artery had almost ceased to pulsate, and a hard tender, fusiform mass replaced the previously dilated and pulsating artery. At the same time the sedimentation rate, which had been 6 mm per hour on the day of admission, rose to 34 and 40 mm on the 5th and 6th hospital days. The oral temperature varied between 98.6 and 99.8°F, falling finally to below 99°F on the 11th day, when the sedimentation rate reached 19. The numbness and right shoulder pain gradually improved, the subclavian tenderness disappeared, and a faint pulsation continued to be felt up to the 16th day when the patient was discharged.

Dr John Homans, who saw the patient on two occasions expressed the opinion that sympathetic nerve irritation from the cervical rib had produced brachial arterial spasm, followed by secondary retrograde thrombosis of the subclavian artery. He advised against surgical intervention at that time, since adequate collateral circulation seemed to have developed. He concurred in the opinion that the cerebral episode was in all likelihood the result of embolism from the thrombus that had formed in the subclavian artery.

### DISCUSSION

In this patient, the symptoms of cervical rib had been present for two years and had recurred some months before the cerebral incident. At the time of the embolism, the subclavian arterial pulsation had been present, but an active ascending thromboangitis may be assumed from the diminished radial pulsation and the subsequent development of fever, local tenderness and almost complete obliteration of the pulse in the right subclavian artery. The sudden occurrence of left hemiplegia in an otherwise healthy man and its transient character are quite compatible with the diagnosis of a small cerebral embolism. This represents another case in which a thrombus, originating in the right axillary or subclavian artery, propagated itself toward the right common carotid whence a small fragment broke off to lodge in a branch of the right middle cerebral artery and thereby produced a transitory left hemiplegia.

In every reported case of this unusual syndrome, the thrombosis occurred in the right subclavian or axillary artery, and the cerebral lesion was also right sided. This is readily explained by the fact that only on the right does the common carotid originate with the subclavian from the innominate artery, so that only on this side of the body would a retrograde thrombus or embolus be caught in the

carotid blood stream and carried to the brain. Should thrombosis occur in the left subclavian artery, emboli would be carried into the aorta and lodge in places less likely to produce distinctive symptoms (Fig. 1). Embolic occlusion of the

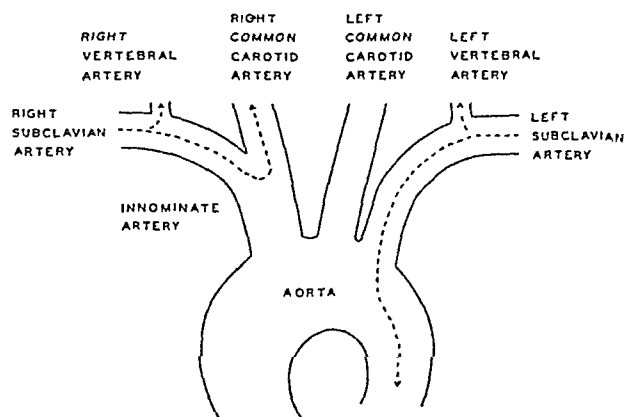


FIGURE 1.

*This diagram illustrates the fact that an embolus from a retrograde thrombus in the right subclavian artery is likelier to enter the cerebral circulation than one from a thrombus in the left subclavian artery.*

basilar arterial branches, as reported by Yates and Guest,<sup>2</sup> could occur from thrombosis in the right or left subclavian artery, since the vertebral artery on both sides originates from the subclavian. The possibility remains that in the other cases embolism also occurred by way of the vertebral artery, passing by means of the posterior communicating artery into the circle of Willis and, finally, entering the middle cerebral vessels, instead of passing directly through the common carotid artery. This explanation is rendered unlikely by the small caliber of the posterior communicating artery, by the frequency with which the right side is involved, and by the infrequency with which emboli are reported to lodge in other branches of the vertebral artery. Furthermore, in Smith's<sup>3</sup> case, in which autopsy was performed, there was definite proof that the pathway of embolism was the carotid and not the vertebral artery.

The only other findings common to all the cases reported were a history of symptoms of cervical rib or vascular insufficiency over a period of a few months to six years, and an absence of right brachial or radial pulsation at the time of the cerebral accident. In most cases, the subclavian artery had also ceased to pulsate, but in one patient, thrombosis of this vessel did not take place until after the hemiplegia had developed. In no case did definite evidence of ascending thrombosis or thromboangiitis in the right subclavian artery occur immediately prior to the embolism.

It should be emphasized that this complication

of subclavian thrombosis is uncommon. In the files of the Peter Bent Brigham Hospital and the Boston City Hospital, no similar cases could be found, and the few isolated reports in the literature bear further witness to its rarity.

Although the conception of embolism originating from retrograde thrombosis of an obstructed artery is somewhat unusual, the occurrence of emboli from mural thrombi located in the wall of large arteries or aneurysms has frequently been reported. Lewis and Pickering<sup>6</sup> suggest that some of the peripheral symptoms of cervical rib may be due to small emboli coming from mural thrombi in the compressed wall of the subclavian artery. In the case reported by Girode et al.,<sup>7</sup> a fatal embolism at the aortic bifurcation was traced at autopsy to a thrombus in an aneurysm of the abdominal aorta. In Marcus's<sup>8</sup> patient, mural thrombosis in the descending aorta gave rise to four distinct embolic episodes. Wood<sup>9</sup> described a young man who complained of pain in the right shoulder, developed suddenly a cold pulseless right extremity, and died fourteen hours later following a left hemiplegia. At post-mortem examination, a walnut-sized aneurysm was found just proximal to the origin of the right common carotid artery, and thrombi were found in the right axillary artery and in the circle of Willis. Unfortunately, the report does not state whether a thrombus was found in the aneurysmal sac, which might have given rise to two separate emboli, whether the axillary thrombus might have been the source of a cerebral embolus, or whether both arteries developed thrombosis in situ.

## SUMMARY

A case of cervical rib is described in which retrograde subclavian arterial thrombosis, embolism to the right middle cerebral artery and a resultant left hemiplegia developed. Five cases with a similar syndrome, which have been reported in the literature, are reviewed.

## REFERENCES

1. Symonds C P. Two cases of thrombosis of subclavian artery, with contralateral hemiplegia of sudden onset, probably embolic. *Brain* 50:259, 1927.
2. Yates A. G., and Guest, D. Cerebral embolism due to an ununited fracture of the clavicle and subclavian thrombosis. *Lancet* 2:225, 1928.
3. Smith, G. W. Aneurysm of the axillary artery with cerebral embolus a case report. *U S Nat. M. Bull.* 39:551, 1941.
4. Gould, A. P. A case of spreading obliterative arteritis. *Tr. Clin Soc* 17:95-104, 1884.
5. *Idem*. Further notes of a case of obliterative arteritis. *Tr. Clin Soc* 20:252, 1887.
6. Lewis, T., and Pickering, G. W. Observations upon maladies in which the blood supply to digits ceases intermittently or permanently, and upon bilateral gangrene of digits observations relevant to so-called "Raynaud's disease." *Clin. Sc.* 1:327-366, 1934.
7. Girode, Moricard, and Brouet. Embolie de la bifurcation aortique chez un sujet syphilitique porteur d'un anévrysme de l'aorte abdominale. Intervention chirurgicale tardive. *Ann. d'anat. path.* 10:616-619, 1933.
8. Marcus, M. Wandständiger Thrombus der Aorta als Ursache vielfacher Arterienembolien des grossen Kreislaufs. *Deutsche Zeitschr. f. Chir.* 235:766-769, 1932.
9. Wood, O. T. Clinical significance and differential diagnosis of shoulder pain. *New Internat. Clin.* 1:18-24, 1941.

MEDICAL DISCHARGES FROM MILITARY SERVICE<sup>1</sup>

## A Report of Six Hundred Cases

DAVID J. FLICKER, M.D.,<sup>†</sup> AND OLON H. COLEMAN, M.D.<sup>‡</sup>

CAMP BLANDING, FLORIDA

ARMY requirements provide that, when an enlisted man because of physical disability has become permanently unfitted for military service, he be retained in a hospital until his physical condition has reached such a point that he will not be benefited by further treatment in a military hospital.<sup>1</sup> When he has reached this condition of maximum benefit, a C. D. D. (Certificate of Disability for Discharge<sup>2</sup>) is prepared by his immediate commanding officer and forwarded to the commanding officer of the hospital, station or regiment in which the enlisted man is serving. On receipt of this certificate, the commanding officer convenes a board of medical officers, usually three, to examine the enlisted man critically and to enter on his certificate the required data. These data must include the origin and degree of disability, and must describe particularly the disability, wound or disease, and the extent to which it deprives the enlisted man of the use of any limb or faculty or affects his health, strength, activity, constitution or capacity to labor.

Such discharge is not recommended by this board when in their opinion the enlisted man, although mentally responsible, is incompetent or does not possess the required degree of adaptability for the military service, or gives evidence of habits or traits of character that make his retention in the service undesirable, and when the underlying cause for these characteristics is constitutional psychopathic state, morose state, mental deficiency, chronic alcoholism or drug addiction.<sup>3</sup> If, however, it is the opinion of the board of medical officers that the enlisted man is not mentally responsible, he is discharged with a certificate and in accordance to Army Regulation 600-500.

An honorable discharge<sup>4</sup> from the Army of the United States is given if the disability is received in line of duty. If the disability is the result of a man's own misconduct, occurring since or prior to enlistment, he is given a "blue" discharge. This is neither a dishonorable nor an honorable discharge. It is a discharge without honor. If the disability was noted on the enlistment paper, how-

ever, or the soldier merits an honorable discharge by reason of honest and faithful service for one or more enlistments since the occurrence of the disease that resulted in the disability, an honorable discharge is given.

It is apparent, therefore, that by the certificates of disability for discharge the Army may dispose of men who have slipped by induction boards and are unfit for military service.

It is also possible to return to civilian life soldiers who, because of mishap, are so injured or afflicted with disease as to be no longer of value in a fighting machine. As a matter of practice, the enlisted man is kept in the hospital wards until a complete and detailed medical workup is obtained. This may, and usually does, include many consultations, laboratory tests, x-ray films and whatever else the staff physicians deem advisable. The physician works with the ease obtainable in pure medical practice; and since no expense is spared, no financial problems are involved. All the medical knowledge, ability and equipment and all the nursing at the command of the hospital are utilized. Every effort is expended to return the soldier to the effective list. However, cases of failure perforce occur. Perhaps the man was admitted to the Army in error. He may not possess the proper qualifications for a soldier. He may have shown, subsequent to induction, epileptic seizures or psychotic or psychoneurotic traits that the inducing physicians were unable to detect. Before induction he may have had flat feet, nonsymptomatic, that subsequently started to cause pain; he may have been a good soldier and been injured with resultant loss of a limb or an eye or he may suddenly be discovered to have diabetes or other serious illness. These are but a few of thousands of possible situations that may necessitate relieving the soldier from military duty.

In Camp Blanding, we have been presented with an opportunity to study personnel from different parts of the country from the time of their induction into the Federal service. We have two divisions: the Thirty-first, or Dixie Division, comprises troops from Florida, Georgia, Mississippi, Alabama and Louisiana; the Forty-third, or New England Division, consists of troops from the six New England states. We present herewith the compiled abstracted data on the first 600 men to

<sup>1</sup>From the Station Hospital Camp Blanding (Colonel) Luther R. Foust (Camp Surgeon).

<sup>2</sup>Captain Medical Corps Reserve, Army of the United States.

<sup>3</sup>Major Medical Corps Reserve, Army of the United States Regular, 52nd Hospital, Camp Blanding.

<sup>4</sup>This group of cases is disposed of according to Army Regulation 615 3/4 Section VIII.



receive certificates. This survey includes the period from January 15 to July 21, 1941, inclusive.

Rate of Granting Certificates

Figure 1 shows how the rate of certificates has risen since the opening of the camp. The slow on-

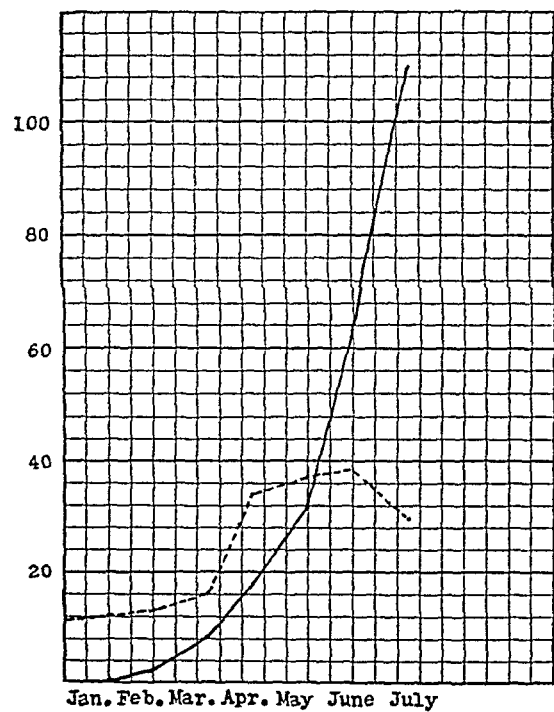


FIGURE 1. Rate of C.D.D. Discharges.

The solid line represents the rates of discharge per thousand per annum; the dotted line, the camp strength in thousands.

set, with the sharp rise, must be interpreted as related to the difficulties encountered in getting the hospital routine established and in getting a smooth-

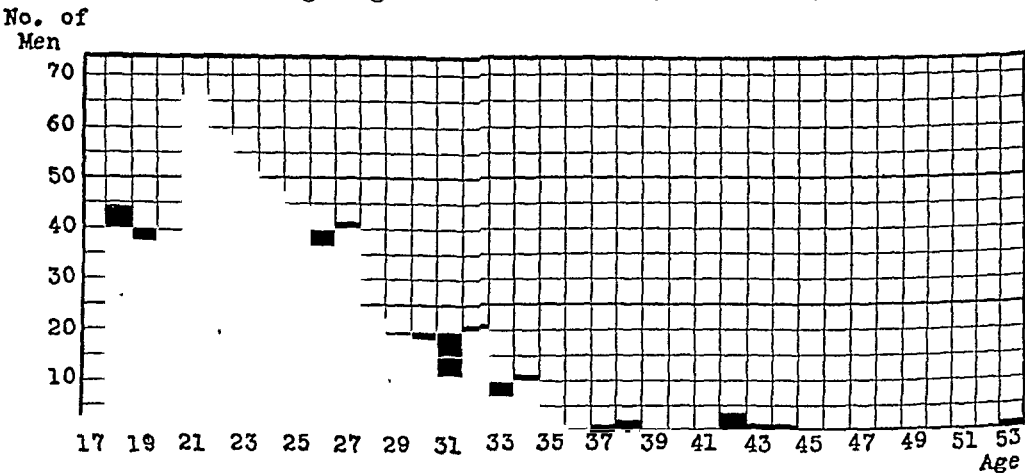


FIGURE 2. Age When Discharged.

ly functioning organization for the disposal of patients entitled to certificates. It must be remembered that the divisions involved were National Guard divisions that had insufficient knowledge of

Army regulations for the disposal of casualties. Many certificates were slowed down in the technicalities of regulations. Another factor of considerable weight is that no competent psychiatrist arrived in Camp Blanding until about March 15. This fact also accounts for the high percentage of organic cases in comparison with cases in which the psychic factors were of greatest importance. Of the 600 discharges, 464 disabilities (77.3 per cent) were listed as organic. The diagnoses "flat feet," "sacroiliac disease," "gastritis," and "tachycardia, persistent, etiology unknown," figured largely. Perusal of the charts revealed that many of these cases might more properly have been called neurocirculatory asthenia, gastric neuroses, psychogenic backache and so forth. One hundred and thirty-six men, or 22.7 per cent, were discharged for psychiatric reasons. These included such diagnoses as "mental deficiency" (42), "psychoneurosis" (63), "psychosis" (23) and others (8). Subsequent figures have shown that the discharges from psychiatric causes in a peacetime army may even exceed those from organic causes.<sup>4</sup>

Age

Despite popular conception to the contrary, the number of discharges did not increase with age, and the ratio of certificates to the number of men in each age group was quite constant. Figure 2 shows the actual number of men discharged in each age group. Figure 3 shows the percentage of discharges of each age group. This is compared with the percentage of men of each age in a random sample of 3000 soldiers.

Duration of Service

How long is it before a soldier manifests signs indicating his inability to fit into the military or-

ganization? How long does it take the Army to determine that a man is unfit to be a soldier? Figure 4 shows our findings. The significant fact is that the peak is at three months. Since in most cases

about six weeks elapse in the machinery of obtaining a certificate (complete hospital workup, holding of a board and obtaining of necessary endorsements), it can readily be seen that most men who are going to break down do so rapidly and are rather promptly recognized. Furthermore, in the reported cases, we believe that the lag after three

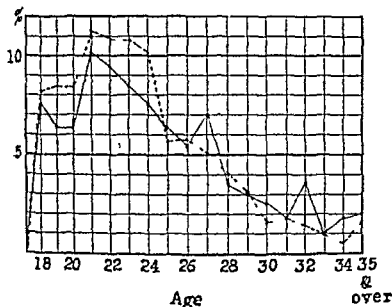


FIGURE 3 Percentages of Discharge by Age

The solid line represents the percentages of discharge by age, the dotted line, the percentages of camp population by age

months is attributable to the newness of the divisions in Federal service and the slowness in the establishment of the routine for obtaining certificates. It must be borne in mind that these divisions until quite recently were in the service of the various states and that the men trained one or two nights per week and, possibly, three weeks during

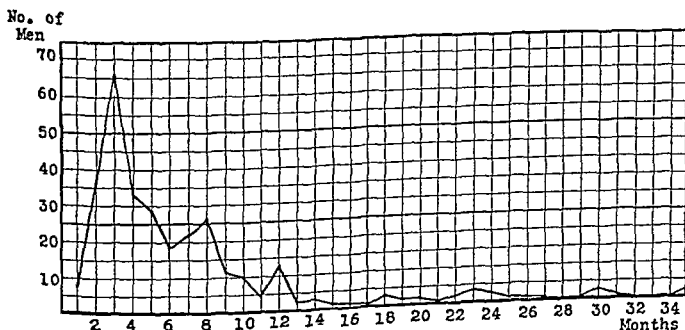


FIGURE 4 Months of Service before C D D

the summer each year. They had, therefore, a limited experience in the methods of the Army.

#### Previous Occupation

It was rather difficult to arrive at any definite conclusions regarding previous occupations. In the first place, each grouping had to be quite arbitrary.

Whether a farmer is to be considered an unskilled, semiskilled or skilled laborer is a moot point, and whether a truck driver who handles a trailer truck is unskilled or skilled is equally debatable. However, these questions were solved as seemed justifiable in each particular case. College students, lawyers, veterinarians, a physician (who was discharged for epilepsy and later committed suicide), a doctor of philosophy in chemistry and a chemist were in the professional group; merchants, store clerks and salesmen were placed in the business group. Table 1 shows the number

TABLE 1 Occupations of Men Receiving Certificates of Disability for Discharge

OCCUPATION	NO DISCHARGED	PERCENTAGE OF TOTAL DISCHARGES	PERCENTAGE OF 3000 SOLDIERS
Unskilled labor	244	37.0	28.7
Semi skilled labor	103	17.1	23.1
Skilled labor	131	21.8	20.2
Business	50	15.0	16.4
Professional	4	.6	9.6

of men in each occupational group who were discharged, the percentage each group contributed to the 600 discharges, and the percentage of men in each occupational group as taken from the previously mentioned sample of 3000 soldiers. It is apparent that the more educated and highly trained the person, the better his adaptability and the greater the likelihood of his being a successful soldier. It reminds one of a statement attributed to General Pershing, "The best citizens make the best soldiers." Furthermore, there was a considerable

difference in the reasons for the failures of the educated and uneducated.<sup>4</sup>

#### Rank

Among the noncommissioned officers, selection, both psychologic and physical, had already taken place to a great extent. Those who were dis-

charged usually had quite a duration of service and received certificates for physical disabilities that were frequently engendered in line of service. Very few of these noncommissioned officers were discharged with such diagnoses as "psychoneurosis." They were less frequently discharged, from a percentage basis in relation to their numbers, than the privates, and the ratio decreased with the increase in rank. This is quite obvious in Table 2, which shows the number of men in

TABLE 2. *Ranks of Men Discharged.*

RANK	No. Discharged	PERCENTAGE OF TOTAL DISCHARGES	AVERAGE PERCENTAGE IN ARMY
Private . . . . .	479	78.5	52.0
Private, first class . . . . .	57	9.5	30.0
Corporal . . . . .	38	6.3	10.0
Sergeant . . . . .	26	4.3	8.0

each grade discharged, the percentage of the discharges in each rank and the average percentage of men in each rank in the Army as a whole.

Type of Service

This camp is essentially an infantry camp, possessing only one field-artillery brigade and no cavalry units. Other troops include military police, a hospital detachment, a quartermaster corps and similar corps-area-service command troops. No significant relation could be found between the number of discharges and the type of military service performed, these figures standing approximately in direct ratio to the number of troops engaged. Thus, 400 certificates were contributed by the infantry, 88 by the artillery, and 112 by other groups. The type of military service could not be regarded as a contributory factor to medical discharge.

Urban versus Rural Population

Arbitrarily selecting all municipalities listed in the 1941 *World Almanac* that contain 2500 inhabitants or over as representing urban life, we divided the men in accordance with rural or urban origin (Table 3). The percentage of discharges

TABLE 3. *Discharges among Men from Urban and Rural Sections.*

SECTION	No. Discharged	PERCENTAGE OF TOTAL DISCHARGES	PERCENTAGE OF 3000 SOLDIERS
Urban . . . . .	108	18.0	32.4
Rural . . . . .	492	82.0	67.6

among men from rural sections was all out of proportion to the percentage of such troops in the Army, and leads one to the assumption that the

"stalwart farmer boy" may not be so good a soldier as his city brother.

Incidence by States

On July 25, the comparative strength of the two divisions was: the Thirty-first, 17,942 men, and the Forty-third, 16,483 men. By that date, there had been 149 certificates from the Forty-third and 410 from the Thirty-first Division, 41 being listed as from "other troops." Reduced to percentages, it had become necessary for the Thirty-first Division

TABLE 4. *Discharges by Sections and States.*

SECTION	TOTAL No. OF MEN	No. OF DISCHARGES
New England (43rd Division).	16,483	149 (0.64%)
Maine . . . . .		20
New Hampshire . . . . .		4
Vermont . . . . .		31
Massachusetts . . . . .		1
Rhode Island . . . . .		11
Connecticut . . . . .		82
South (31st Division) . . . . .	17,942	410 (2.29%)
Georgia . . . . .		17
Florida . . . . .		130
Alabama . . . . .		81
Mississippi . . . . .		90
Louisiana . . . . .		92

to discharge 2.29 per cent of its personnel whereas the Forty-third Division had released only 0.84 per cent. The number of cases by states is shown in Table 4. These are the states in which the men were inducted into military service.

Line of Duty

Of the 600 cases reported, only 8 were marked as "line-of-duty" discharges. In all the others, the notation was made that the disease or disability "existed prior to enlistment."

SUMMARY

An analysis of the first 600 cases relieved from duty at Camp Blanding under the Army regulation providing for certificates of disability for discharge is presented. The rate of discharges, the relation of organic to psychic factors as causes of disability, the age of enlisted men at the time, the duration of service prior to medical discharge, the relation of previous earned rank and type of service, whether the cases were urban or rural, and, finally, the geographical distribution by sections and states are given.

These statistics were collected during the formative period of the camp, and further studies may show substantial changes in some of these factors.

REFERENCES

1. Army Regulation 615-360, Section II.  
2. War Department, Adjutant General's Office, Form 40.  
3. War Department, Adjutant General's Office, Form 55.  
4. Unpublished data.

# ANTHRAX: REPORT OF A FATAL CASE INVOLVING THE CUTANEOUS AND GASTROINTESTINAL SYSTEMS\*

WILFRED D. MACDONALD, M.D.†

WORCESTER, MASSACHUSETTS

**H**UMAN anthrax, usually involving the skin is still an industrial hazard confronting workers in tanneries and wool industries and to a certain extent agricultural laborers. Since most industrial anthrax is of the cutaneous type and the reports of internal anthrax (pulmonary and gastrointestinal) in the literature are so few, the following case is presented.

## CASE REPORT

H S, a 38-year-old man, was admitted to the hospital on June 17, 1941, obviously dangerously ill. He had been employed for years in a Worcester brush factory where he handled bristles imported from China, India and Manchukuo.

Four days before admission the patient was seen at home by his physician who treated him for sore throat and swelling of the lymph nodes on the right side of the neck. He did not seem acutely ill at this time. However, he appeared much worse each day of his illness and a day prior to admission his face was markedly swollen, the pulse was of poor quality, and the temperature was subnormal. Moreover, the abdomen was tense and distended and very tender to pressure.

On the morning of admission the patient's condition grew critical at home, and he was referred to the Belmont Hospital with a tentative diagnosis of mumps. Meanwhile a pustule on his forehead aroused the suspicion of anthrax.

On admission the patient's temperature was 97.0°F and no pulse could be detected at the wrist. The respirations were 40 per minute and very labored. The patient was drenched in perspiration, the lips were cyanotic and there was a generalized, mottled cyanosis of the skin. He was rational and cooperative and complained of abdominal pain, inability to catch his breath and weakness in the forehead, just above the right eyebrow, was an area of redness about the size of a five-cent piece. This lesion was raised and indurated. Topping the lesion was a 4 mm. pustule with a central umbilicated hemorrhagic and necrotic area. The tongue was dry and heavily coated. The roof of the mouth was studded with eight to ten tiny yellow pustules. The pharynx was red and injected and heavy, greenish yellow exudate was noted in the postnasal space. There was a large brawny induration of the left side of the face and neck. This mass was hard and no pitting edema or fluctuation could be felt. The heart sounds were weak, —barely audible— and no murmurs were heard. The blood pressure could not be read. Nothing abnormal was found in the lungs. The abdomen was tense, tympanic and markedly distended with tenderness, with spasm over the entire upper abdomen. No palpable masses or viscera were felt. The extremities were mottled in appearance and very cold to palpation. There were no neurologic changes.

The diagnosis on admission was anthrax cutaneous type, gastrointestinal anthrax and anthrax bacteremia. The diagnosis was tentatively confirmed by direct smear of the purulent material from the lesion on the forehead. The blood culture taken on admission showed a heavy growth of *Bacillus anthracis* in 36 hours.

The patient was immediately treated for shock. He was given 1000 cc of 5 per cent glucose by vein and shortly thereafter 2 gm of sodium sulfapyridine also by vein. As soon as a suitable donor could be obtained the patient received 500 cc of citrated blood. Meanwhile a request was sent to Boston for 300 cc of specific anti-serum. After the transfusion the patient improved for a while but the pulse did not become perceptible. He was catheterized because of inability to void for about a day at home but only a small amount (70 to 25 cc) of very concentrated urine was obtained.

Examination of the blood showed a red-cell count of 5,500,000 with a hemoglobin of 90 per cent (Sahli), and a white cell count of 10,600. The urine showed a specific gravity of 1.073, acid reaction, the slightest possible trace of albumin and no sugar. The sediment showed a few hyaline casts and a few red and white blood cells per high power field. Smears and cultures of the lesion on the forehead were positive for *B. anthracis*. The nonprotein nitrogen was 19 mg and the blood sugar 143 mg per 100 cc.

The patient became progressively worse. He developed delirium about 5 hours after admission and died 1 hour later before serum could be obtained. Prior to expiration the patient vomited a large amount of coffee grounds, material mixed with bright red blood and he had a terminal rise in temperature to 103.0°F.

**Autopsy** (performed by Dr. Raymond Goodale of the Worcester City Hospital). There was an elevated skin lesion just above the right eyebrow. This lesion measured 1.2 cm in diameter with a 3.0 mm central depression. In addition a few golden yellow lesions were noted on the hard palate.

The lymph nodes on the right side of the neck were enlarged and the surrounding edema extended down to the clavicle on that side. The organs of the chest were grossly normal.

The abdominal cavity contained about 500 cc of cloudy, amber colored fluid. The mesentery contained a few hemorrhagic areas in which the fat was swollen so that it measured 5 cm in thickness.

The thoracic esophagus was normal. The stomach appeared grossly normal but contained 50 cc of coffee grounds material. Just below the ampulla of Vater was an edematous area in the mucosa measuring 6.0 cm in diameter and giving the intestinal wall a total thickness of 1.5 cm. The lesion was red and there was a glistening mucinous appearance on section. In the lower jejunum 170 cm from the duodenum was the second lesion which measured 1 cm in diameter. The third lesion located 200 cm above the ileocecal valve, measured 1.5 cm in diameter. The fourth lesion was 190 cm above the ileocecal valve and also measured 1.5 cm in diameter. The fifth and largest lesion which was located 170 cm above

\* From the Department of Contagious Diseases, Belmont Hospital.  
† Chief of the Department of Contagious Diseases, Belmont Hospital.

the ileocecal valve, measured 18 cm. in length; it was intensely red and swollen, and the mucosa showed signs of necrosis (Fig. 1). The final lesion was located 120 cm from the ileocecal valve, and was 15 cm. long; the mucosa was pink and swollen but no hemorrhage or necrosis was present. All lesions presented a mucinous appearance on section.

tract was undoubtedly the swallowing of large numbers of the spores. Lucchesi<sup>1</sup> points out that the mouth may be infected by contaminated hands.

The fatality rate from cutaneous anthrax is still high, 16 per cent being average mortality for the cases reported during the five-year period 1934-

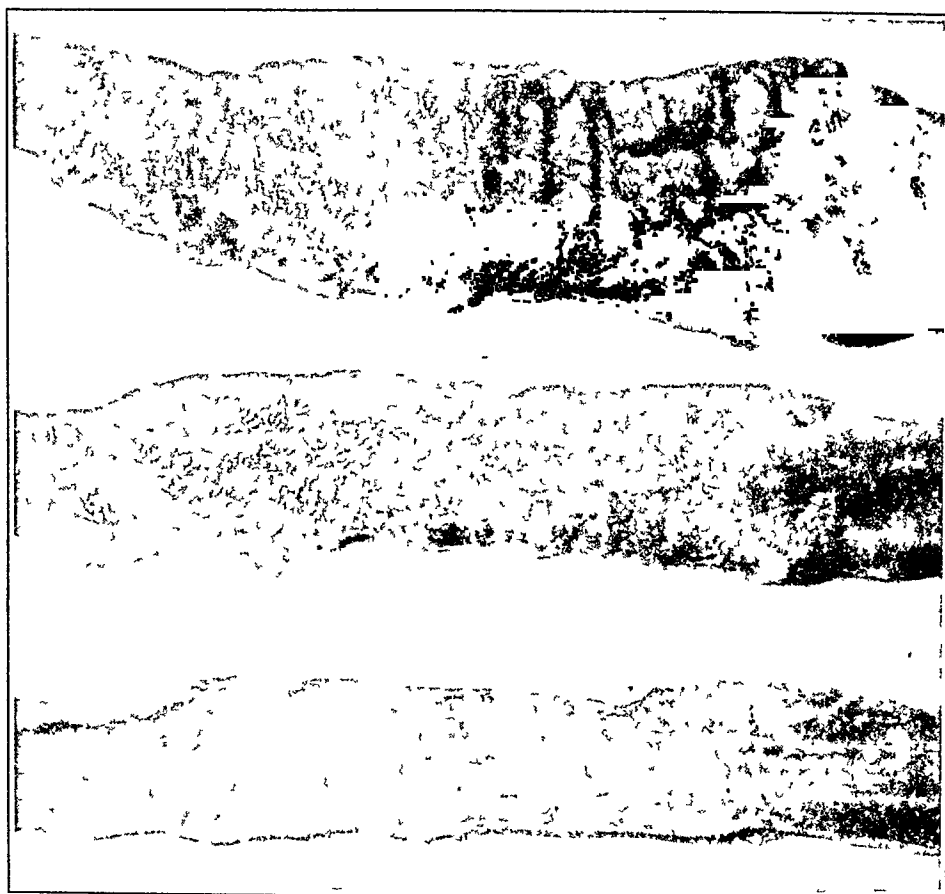


FIGURE 1. *Lesions of the Small Bowel.*

*The upper specimen is a section of small bowel showing maximum involvement, with edema, hemorrhagic changes and early necrosis, the middle one shows the earlier changes, which consist of edema, a gelatinous exudate and some hemorrhagic changes, with no necrosis. The lower one is a section of normal small bowel.*

Anthrax bacilli were recovered from the cultures of the pus from the lesion on the forehead, of the free abdominal fluid and of the blood removed from the right auricle.

Microscopic examination of the mesenteric lymph nodes showed an acute, hemorrhagic adenitis, there were acute inflammation and edema of the ileum, a few anthrax bacilli being present.

#### DISCUSSION

This case represents a massive inoculation with *B. anthracis*. The cutaneous lesion occurs usually after contamination of an apparently healthy skin with spores of the anthrax bacillus. In the case presented, there was no history of previous trauma to the skin. Most writers, however, postulate a break in the skin before infection can take place.

The mode of invasion of the gastrointestinal

1938. However, this represents a 6 per cent reduction from the previous five-year period. Internal anthrax, on the other hand, is almost always fatal. Eurich<sup>2</sup> reports 23 cases of pulmonary anthrax that ended fatally. He had seen but one case of gastro-intestinal anthrax. Moreover, the recent literature does not report a single case of recovery from gastrointestinal anthrax. There is a possibility, however, that the outlook for internal infection will improve with newer methods of treatment, as evidenced by the recent report of Lucchesi and Gildersleeve,<sup>3</sup> who report 2 cases of recovery following anthrax bacteremia. Moreover, one of the cases was of the pulmonary type, which is usually rapidly fatal.

In the treatment of anthrax, several features stand out clearly. The recent investigators are apparently in agreement that local incision and excision of the anthrax pustule is contraindicated unless the lesion is very small and easily accessible for surgery. Moreover, the practice of local injection of serums around the lesion has been discontinued in most clinics.

Serotherapy, given intravenously and occasionally intramuscularly, seems to be indicated in all cases of anthrax. The method used is fairly large doses (100 to 300 cc.) given at twenty-four-hour intervals over a three-day period.<sup>3</sup> Neoarsphenamine given in 0.6-gm. to 0.9-gm. doses over this same three-day period has proved to be a valuable adjunct in treatment<sup>3</sup>; this may permit reduction in the dose of serum.

Recently, sulfanilamide and sulfapyridine have been used in the therapy of anthrax. In guinea pigs, according to Mitchell, Walker and McKercher,<sup>4</sup> sulfanilamide seems to control the spread of the anthrax infection; however, this drug has not

been used in a sufficient number of human cases to provide definite conclusions of its value. Bonnar<sup>5</sup> reports recoveries in 2 critical cases in which sulfapyridine in conjunction with serum and neoarsphenamine was used.

#### SUMMARY AND CONCLUSIONS

A fatal case of internal anthrax with bacteremia is reported, with autopsy findings.

Anthrax still remains an occupational hazard to workers in wool, hair and hides, in spite of rigid control of imported materials.

The prognosis of internal anthrax is grave in spite of the excellent results obtained in the therapy of cutaneous anthrax with specific serum and neoarsphenamine.

#### REFERENCES

- 1 Lucchesi, P. F. Serum treatment of nineteen cases of anthrax including one of external, internal and bacteremic type. *Am. J. M. Sc.* 183:795-802, 1932.
- 2 Torrich, T. W. Some notes on industrial anthrax its diagnosis and treatment. *Brit. M. J.* 2:50-53, 1933.
- 3 Lucchesi, P. F., and Gunderslee, N. The treatment of anthrax. *J. A. M. A.* 116:1506-1508, 1941.
- 4 Mitchell, C. A., Walker, R. V. L., and McKercher, D. G. The use of sulfanilamide in anthrax. *Canad. J. Comp. Med.* 3:119-130, 1939.
- 5 Bonnar, W. Sulphapyridine in human anthrax. *Brit. M. J.* 1:139, 1940.

## MEDICAL PROGRESS

### VASCULAR DISORDERS OF THE EXTREMITIES (Concluded)

JOHN HOMANS, M.D.\*

BOSTON

#### POST-TRAUMATIC PAIN COMPLEXES

UNDER the titles "post-traumatic pain syndromes" (Livingston<sup>37</sup>), "reflex dystrophy of the extremities" (de Takats<sup>38</sup>), "trophoneuroses" and many others, these peculiar painful states have long been looked at askance by the profession in general as functional, perhaps hysterical, disorders. Recently, Homans<sup>39</sup> has discussed them under the title "minor causalgia" and has called attention to the fact that similar disorders may follow inflammatory thrombophlebitis of the legs. That painful, edematous states associated with paresthesia of the skin may arise from thrombophlebitis tends to confirm earlier impressions that such syndromes represent a vicious reflex arising from irritated peripheral vascular sensory-nerve fibers.

The minor causalgias are usually insurance problems and as such have considerable economic importance. The initial injury is usually trifling. A blow on the hand, forearm or foot, the wound of

a thorn, a burn, a frostbite, a minor fracture or sprain, a felon, a "milk leg," any of these may establish the reflex disorder. The hand is oftenest affected. Some part of it, usually a roughly anatomic field of one or more great nerves, is "dull" to pinprick, cool to the touch, slightly edematous (knuckle markings lost) and faintly bluish. The part feels "stiff," the grip is lost, and there may be some sensitive area—trigger point—that causes the patient to protect the part from all contacts. The severity and persistence of the causalgia vary greatly, but a hysterical element is rarely present and most of the victims desire to work.

The causalgia can usually be cured by the breaking up of the reflex, even temporarily, by the interruption of sensory impulses at the trigger point (Livingston), on the principal artery leading from the part, in the somatic nerve serving the part (Livingston) or in the sympathetic chain at the root of the affected limb. A single injection of procaine may cure. Repeated injections have a progressively good effect. Gentle measures and persistence are usually rewarded. Probably, surgery should not go beyond periarterial sympathectomy or paravertebral sympathectomy, al-

\*Reprints of articles in this series are not available for distribution, but the articles will be published in book form. The current volume is *Medical Progress Annual, 1940* (Springfield, Illinois: Charles C. Thomas Company, 1941, \$4.00).

\*Consultant, Peter Bent Brigham Hospital and Joseph H. Pratt Diagnostic Hospital, Boston.

though excision of a sensitive scar or sinus is sometimes successful.

### THROMBOSIS IN DEEP VEINS OF EXTREMITIES

Within the last few years, the venous thromboses in the lower limbs have been separated into two classes: the quiet, nonobstructive, embolus-threatening sort, or *phlebothrombosis* (Ochsner and DeBakey<sup>40</sup>), and the outspoken, inflammatory, obstructive sort, or *thrombophlebitis*. The pathological studies of Neumann,<sup>41</sup> Frykholm<sup>42</sup> and Hunter et al.<sup>43</sup> have proved that in fatal cases (pulmonary embolism) the thrombosis, almost necessarily the quiet phlebothrombosis, originated in the venous plexuses among the muscles, particularly in those of the calf but sometimes in those of the foot or thigh. Venographic examinations, instigated by dos Santos<sup>44</sup> and greatly developed by Bauer,<sup>45</sup> have shown how the common, quiet process, complicating injury, operation or disease, or even appearing during active life (Homans<sup>46</sup>), may remain local or progress into the femoral vein. Here it may form a long, loose, fatal embolus or work its way centrally in a lightly adherent, nonobstructing form into the upper femoral or external iliac vein, or actually fill and block the latter vein, causing the familiar phlegmasia alba dolens of thrombophlebitis.

#### *Phlebothrombosis*

This relatively quiet process may be utterly silent until a serious embolism occurs. Or it may cause lameness (on walking), pain in the calf, full, slightly tense, tender muscles, discomfort on forced dorsiflexion — the dorsiflexion sign — and a varying degree of edema and cyanosis, which may be absent on elevation and only evident on dependency.

There is some difference of opinion concerning treatment. The statistical figures of Barker, Nygaard, Walters and Priestley<sup>47</sup> indicate that about one person in twenty in whom thrombosis is *recognized* will suffer an embolism whether or not fatal; and that one person in five, having experienced a pulmonary infarction, will die of a later embolism. As a result of their clinical experiences, Fine and Sears<sup>48</sup> recommend, as a routine procedure, exploring the femoral vein, to head off the embolism, remove the clot and so forth, whenever a diagnosis is made. Welch and Faxon<sup>49</sup> favor it. Welch, Faxon and McGahey,<sup>50</sup> by combining the routine use of venography with special clinical observations, have determined to their satisfaction the indications for femoral exploration and the management of thrombosis at various levels and stages. Homans<sup>51</sup> prefers conservative treatment in early cases, but opens and divides the

femoral or one of the iliac veins when embolism or recurrence of symptoms (after nonoperative treatment) indicates that healing without further accident is unlikely. For conservative treatment, he recommends 6-inch elevation of the foot of the bed, freedom of movement, no ice bag, no bending at the hip and, after ten to fourteen days of such elevation, gradual resumption of activity in a semielastic bandage.

The value of heparin is difficult to assess. Murray and Best<sup>52</sup> have shown that routine postoperative heparinization heads off thrombosis. Murray<sup>53</sup> points out that in a considerable series of cases, heparinization, instituted only after pulmonary infarction had already occurred, prevented further embolism\* (an important observation in view of the percentage of deaths following a preliminary infarction recorded by Barker et al.<sup>47</sup>). Heparin may be given as a continuous intravenous drip (Murray and Best) or every four hours, in a dosage of about 60 mg. of purified heparin, constantly checked by the clotting time (capillary-tube method). The expense is at least seven or eight dollars a day even without special nursing. When surgery is not available and especially when expense is not a problem, heparinization seems indicated. A clotting time of ten to twenty-five minutes should be maintained for three to five days and then tapered off, to avoid the danger of recurrent thrombosis.

Dicoumarin, whose use is in the experimental stage, has recently been put forward as an anticoagulant. Provided it is efficient and not harmful, the fact that it can be given by mouth gives it an advantage over heparin. Unlike heparin, whose action can be stopped immediately on neutralization by protamine, dicoumarin, once in the circulation, cannot be neutralized, and transfusion of blood is not always a satisfactory means of control of the dicoumarin effect. Dicoumarin lengthens the clotting time materially only after being administered for several days, and its action continues for several days after it has ceased to be given (Davidson<sup>54</sup>). Thus, present information indicates that caution should be used in the acceptance of dicoumarin as a satisfactory substitute for heparin in such situations as those for which heparin is now known to be valuable.

#### *Thrombophlebitis*

Irrespective of its origin, that is, whether it begins in a thrombosis low in the leg, in the uterine veins or locally in the femoroiliac region, thrombophlebitis, phlegmasia alba dolens or "milk leg" is an obstructive process in which an inflammatory exudate often surrounds the femoral and iliac veins

\*Although no figures comparable with Murray's are available, deaths from embolism under similar circumstances have occurred in very much smaller series in the experience of other surgeons.

and arteries. Some degree of local arterial spasm, as already noted, results. (Experimentally, the effect on arterial blood flow of a local irritation within and about a large vein is described by DeBakey, Burch and Ochsner.<sup>7</sup>) Also, as a reflex, a diffuse peripheral vasospasm in the arterioles or venules, or both, perhaps, occurs. The resulting edema is due partly to venous obstruction, partly to lymphatic obstruction and partly (in some cases almost exclusively) to the peripheral vasospasm. This list has been Leriche's<sup>56</sup> contribution, and following his observation that lumbar sympathetic procaine block relieves the edema in a remarkable way, Ochsner and DeBakey<sup>7</sup> have fully discussed the pathologic physiology and have popularized this treatment.

The special indications for making use of a sympathetic block are edema, fever and discomfort (as signs of a perivascular irritation). But routine conservative treatment should still be carried on. This consists in elevation of the foot of the bed, without immobilization of the leg, and the use of a heated cradle, to promote vasorelaxation. Ice bags should not be applied. Sympathetic block is most effective if used early. The technic is based on one or another of Labat's<sup>57</sup> methods of securing a paravertebral anesthesia, but adapted by White<sup>9</sup> to reach the sympathetic chain just ventral to the lateral curve of the vertebral body. Ochsner and DeBakey<sup>7</sup> introduce three needles (4 inch lumbar puncture needles, with stylets) through wheels placed respectively about two fingerbreadths (roughly, 4 to 5 cm.) lateral to the midline of the back and opposite the first, second and third lumbar interspaces. Each needle, entering perpendicularly to the plane of the back, should strike a transverse process at a depth of about 4 or 5 cm. The needle is then redirected above or below the process and somewhat medially, meeting next the lateral border of the vertebra. Another readjustment in a more lateral direction carries its point to glide past the vertebral belly for perhaps 1 cm into the region of the gangliated chain. Five to ten cubic centimeters of a 1 per cent procaine solution is injected through each needle.

On the basis of Flothow's<sup>58</sup> recommendation of Lundy's<sup>51</sup> method, others (Reichert,<sup>59</sup> de Takats<sup>60</sup> and Homans<sup>61</sup>) prefer to introduce a 4 inch (for women) or 5 inch (for men) needle, with stylet, 7 cm lateral to the midline opposite the first lumbar interspace. This spot is near the twelfth rib and the outer margin of the erector spinae muscles. The needle is directed toward the midline at an angle of about 35° from the perpendicular. A transverse process may or may not be met at a depth of 4 or 5 cm, the plan being to strike the broad lateral curve of the vertebra at a deeper

level. The needle is then partly withdrawn and redirected more laterally so that it glides just past the vertebral belly. This method increases not only the chances of placing the needle point close to the sympathetic chain which lies toward the front of the vertebra, but also the risk of injuring the aorta (on the left) if the needle is thrust too deeply. However, if it is passed no more than 1 cm beyond its last bony contact and meets no resistance in that last step, an arterial injury is extremely unlikely. Suction should always be made, however, before injection, to make sure no vessel has been entered. If any bleeding occurs, the needle should be withdrawn and reinserted at a higher or lower level.

**Postphlebotic pain complex.** Postphlebotic pain, associated with paresthesia below the knee and some degree of edema and cyanosis, may remain after a femorofemoral thrombophlebitis, a causalgia-like state (Homans<sup>62</sup>). Lumbar sympathetic block, performed during the acute stage of thrombophlebitis, tends to ward off this sequel. In many cases, one or more sympathetic blocks often cure the pain complex itself. The favorable effect of one block should not be allowed to lapse before the next block is given. Thus, in time, even an obstinate process may often be relieved. If not, sympathectomy combined with lysis of adhesions between the iliac vessels on the affected side—or even resection of the diseased vein—is likely to succeed (Leriche and Geisendorff<sup>63</sup>).

## VARICOSE VEINS

### Etiologic Factors

The causative factors of varicose veins have been studied by Adams<sup>64</sup> from the point of view of venous pressures and the effect of valvular incompetence. By means of direct pressure determinations in the normal great saphenous vein, Adams found that the presence of normal valves did not alter the transmission of pressures in the fluid system and that such pressures followed Pascal's law, namely, that "pressure applied to an enclosed fluid is transmitted equally in all directions and acts with equal force on all surfaces." Thus, pressures at any one level represent the weight of the column of blood between that level and the heart. Adams points out that when the patient is upright the resulting high pressures in the leg tend to overstretch the superficial veins unprotected by surrounding muscle. So long as valves remain competent, however, additional pressures from above, caused by straining and lifting, can raise pressure within the saphenous system little if any higher than gravity itself can do. But once the valves become incompetent, the effect of straining and lifting is to raise superficial venous



pressure in varicose veins to pathologic levels. In such veins, as is well known, pressure may rise to high arterial levels. Adams then makes some interesting inferences:

"Recannulization" (Adams's word) will occur after treatment by injection unless a high preliminary division is carried out. High division should not be condemned because pressures in the remaining varices below are not lowered, for all that high division can do is to prevent the additional elevation of pressure due to straining and lifting.

Adams advises the inclusion, in the Trendelenburg test for varicosity, of a consideration of the additional effect, beyond gravity alone, of straining.

Veal and Hussey<sup>67</sup> have made direct examination of pressures in the popliteal veins of pregnant women. They studied especially the effect of exercise to be sure that the engorgement of exercise should be given consideration. As between subjects having respectively normal and varicose (or edematous) legs and between the normal and varicose leg of one pregnant woman, popliteal pressures remained stationary on exercise in the normal leg and rose decidedly in the varicose. They conclude that local venous obstructions within the pelves of some pregnant women have led to varicosities by causing pressures higher than normal in the veins of the legs and that, in selected cases, support of the superficial veins during pregnancy by an elastic stocking or bandage should be advantageous.

Edwards and Edwards<sup>68</sup> have continued their interesting observations on the valves of the veins in the legs. In earlier communications, they<sup>69</sup> discussed the orientation of valves in relation to the body's surface, and the destruction of valves by thrombosis. Now they show how overstretching of the vein's wall causes valves to become useless. They present models of cross sections.

### *Tests for Varicosity*

There is an evident tendency in some clinics to make rather elaborate tests of varicosity. Mahorner and Ochsner<sup>70</sup> have developed elaborations of the Perthes test (observation of the state of filling of superficial veins below an elastic constriction during exercise) to demonstrate obstruction or normalcy of the deep veins and also the presence of incompetent perforating veins at some particular level. So far as the situation of incompetent communicating veins is concerned, the tests of these authors, if intelligently and skillfully performed, show the need for accurate dissection and division of perforating veins in particular patients and particular localities. Experts can well use them for this purpose. (It should be noted that elaborate tests of deep venous obstruction in the presence of

varicose veins are unnecessary. For since varicose veins will not transmit blood upward in the standing position, a normally colored foot in the dependent varicose leg on standing or exercise guarantees a normal deep venous return. Moreover, blocking or removing varicose veins should *always* lighten the load of the deeper system irrespective of the state of that system.)

Pratt<sup>71</sup> regards undiscovered and undivided incompetent communicating veins as a common cause of recurrence after high division and retrograde injection of varicose veins. He considers the Mahorner-Ochsner tests to be "difficult to perform and to interpret and . . . so time consuming that they were not useful in the clinic." He proposes a test that uses the constricting rubber tube about the upper thigh to prevent down-flow through the saphenous vein and applies a bandage from the toes up to the level of this constriction. As the leg is lowered and this bandage is removed by degrees from above, the location of incompetent communicating veins or "blowouts" is revealed. He recommends that such blowouts be surgically corrected. (It is questionable whether the incompetent communicating vein, which Pratt and others describe as a "blowout," affords so direct and open a leak from the deep veins to the varicose superficial ones as is pictured. Anatomic studies made many years ago [Jarjavay<sup>72</sup>] show that alternative routes between the deep and superficial systems are available and are usually able to conduct blood in or out according to local pressures in one system or the other. Thus, although the communicating veins normally conduct blood from surface to depth, some, or all, of them are subject to local pressure influences, through the action of by-passes. Undoubtedly, attention *should* be given to gross leaks outward into varicose veins, and these ought to be considered in planning surgical treatment. But normally high pressures in the postoperative, varicose system are consistent with competent as well as incompetent communicating veins. In this connection, Adams's<sup>66</sup> communication is significant, and pathologically high pressures, that is, on straining and coughing, are far likelier to be re-established, in that part of a varicose system left below a high division, by a reconnection of varicose vessels at the groin than by the communicating veins of the lower leg.)

### ELEPHANTIASIS

A very ingenious and useful contribution to the surgery of elephantiasis has been made by Macey.<sup>73</sup> In a patient with a great congenital hemangiolymphangioma of the arm, a procedure involving the burying of a split graft in the muscle of the fore-

arm and beneath the greatly deformed lymphangiomatous, superficial tissues was attempted. At the end of two weeks, the superficial parts were dissected from the surface of the graft, which had healed perfectly. Only a little loose connective tissue was left between the skin graft and the muscle. Evidently, the forearm and the back of the hand were treated in two stages, although the operator, in describing the first operation, makes the almost incredible statement that the "lymphoedematous, subcutaneous tissue was dissected from the musculature of the forearm in a completely encircling manner."

Undoubtedly, the principle can be applied to the not very uncommon, disabling elephantiasis nostra, or praecox, of the leg, particularly by the aid of the huge and uniform "half" and "three quarter" thickness grafts that Padgett's<sup>74</sup> machine is capable of cutting. If such means prove suitable for covering the deep parts of the whole lower leg, the ankle and the front of the foot, they should prove superior to the procedure of replanting great attached flaps of pure skin on the subaponeurotic structures (Homans<sup>75</sup>), by which half the lower leg and foot can be treated at a sitting. Similar plastic flap operations have been used by Knott,<sup>76</sup> who has had a wide experience with the tropical form of the disease. Knott has also devised most ingenious ways of compressing, by various bandaging devices, the elephantiac leg and finds that, after the leg has been reduced to an approximately normal size, not only are the inflammatory attacks eliminated but a plastic operation is made relatively easy.

Macey's communication, valuable as it is, contains one or two statements that can hardly be allowed to pass unchallenged. He states

The original conception of the Kondoleon operation, that of establishing a communication between the superficial and deep lymphatics, has been discarded and it is now felt that the superficial lymphatics drain directly into the vascular network of the muscles after removal of the deep fascia. On microscopic examination sections of normal muscle have been demonstrated to have abundant lymphatics and from the clinical observation, the lymphatics in the muscles seem involved by the lymphedema.

As to the first of these statements, there is no evidence of any sort that, as a result of a plastic operation, fluids collected between the skin and the deeper structures are carried into spaces between the muscles or that such vascular network as may be present can absorb the highly proteimized tissue fluids of elephantiasis. And as to the second, namely, that abundant lymphatics exist in muscle, there are, it is true, some lymphatics in the intermuscular fibrous tissue of normal persons, but

that lymphatics exist in the muscle proper, there is no convincing proof (Drinker and Yoffey<sup>77</sup>). Apparently, in fully developed elephantiasis, no valved lymphatics are left in the limb. If any tissue fluid passes centrally between the muscles, it must be forwarded by muscular squeezing and pumping. It is not necessary that subaponeurotic lymphatics be present to make a radical plastic operation safe in elephantiasis. In the elephantiac leg, fluid passes through wide spaces in the fibrosed superficial tissues by gravity alone. Such tissue fluids as remain after most of the subcutaneous tissues have been excised probably drift between skin and the underlying muscle, or even in the skin itself, as elastic pressure and gravity direct. Some years ago, Gillies and Fraser<sup>78</sup> implanted pedicled flaps containing lymphatics (from the arm) on the elephantiac leg, with the idea of draining its fluids into a part of the body where absorption was normal. Recently Pratt and Wright<sup>79</sup> have proposed a similar procedure. Even aside from the technical difficulty and dubious success of such elaborate plastic operations, the plan of excising the fluid-bearing, subcutaneous tissues seems decidedly more practical.

311 Beacon Street

REFERENCES

3. Langer, W. K. Post-traumatic pain syndromes: an interpretation of the underlying pathology and physiology. *West J Surg* 46:341 and 476, 1938.

38. Le Takits, G. Pellex dystrophy of the extremities. *Arch Surg* 34:933, 1935.

39. Homans, J. Minor causality following injuries and wounds. *Ann Surg* 113:932-941, 1941. Minor causality in lymphatic disease: vascular syndrome. *New Eng J Med* 223:870-874, 1940.

40. Chamer, A. and Delaney, M. Therapeutic considerations of fibrinolytic and phlebotomy. *New Eng J Med* 223:207-214, 1941.

41. Therapy of phlebotomy and thrombophlebitis. *Arch Surg* 40:708-731, 1940.

42. Neumann, R. Ursprungszentren und Entwicklungsformen der Venen-Thrombose. *Virchows Arch f path Anat* 301:708-735, 1938.

43. Frykholm, R. The pathogenesis and mechanical prophylaxis of venous thrombosis. *Surg Gynec & Obst* 71:307-312, 1940.

44. Hunter, W. C., Sneeden, V. D., Robertson, T. D., and Snyder, G. A. C. Thrombosis of the deep veins of the leg: its clinical significance as exemplified in three hundred and fifty-one autopsies. *Arch Int Med* 68:1-17, 1941.

45. dos Santos, J. C. La phlebographie de recte conception — technique — premiers résultats. *J internat Med* 3:625-669, 1938.

46. Bauer, G. Early diagnosis of venous thrombosis by means of venography and abortive treatment with heparin. *Acta med Scandinavica* 167:136-144, 1941. A venographic study of thrombo-embolic problems. *Acta chir Scandinavica* (Suppl. 61) 84:1-75, 1940.

47. Homans, J. Thrombosis of the deep veins of the lower leg causing pulmonary embolism. *New Eng J Med* 241:993-997, 1934.

48. Barker, N. W., Nygaard, K. H., Walters, W., and Priestley, J. T. A statistical study of postoperative venous thrombosis and pulmonary embolism. I. Incidence in various types of operations. *Proc Staff Meet Mayo Clin* 35:707-713, 1941. II. Predisposing factors. *Ibid* 36:15-19, 1941. III. Time of occurrence during the postoperative period. *Ibid* 36:17-21, 1941. IV. Location of thrombosis relative to that of thrombo-embolism. *Ibid* 36:33-37, 1941.

49. Fine, J. and Sears, J. B. The prophylaxis of pulmonary embolism by division of the femoral vein. *Ann Surg* 114:801-812, 1941.

50. Sears, J. B. Experience with femoral vein ligation for prophylaxis of postoperative pulmonary embolism. *New Eng J Med* 224:131-140, 1941.

51. Welch, C. E. and Faxon, H. H. Thrombophlebitis and pulmonary embolism. *J Am A* 4:117-1502, 1938.

52. Welch, C. E., Faxon, H. H., and McCahey, C. F. The application of venography to the therapy of thrombosis and embolism. *Surgery* (in press).

53. Homans, J. Exploration and division of the femoral and iliac veins in the treatment of thromboembolism. *New Eng J Med* 217:918-919, 1941.

54. Murray, D. W. G. and Rees, C. H. Heparin and thrombosis: present situation. *J Am A* 4:110-118, 1938.

53. Murray, G. Heparin in thrombosis and blood vessel surgery. *Surg., Gynec. & Obst.* 72:340-344, 1941. Heparin in the surgical treatment of blood vessels. *Arch. Surg.* 40:307-325, 1940.
54. Davidson, C. S. Unpublished data.
55. DeBakey, M., Burch, G. E., and Ochsner, A. Effect of chemical irritation of a venous segment on peripheral pulse volume. *Proc. Soc. Exper. Biol. & Med.* 41:585-590, 1939.
56. Leriche, R., and Jung, A. Recherches expérimentales sur les oedèmes chirurgicaux des membres d'origine phlébitique. *J. de chir.* 37:481-495, 1931.
- Leriche, R. Traitement chirurgical des suites éloignées des phlébites et des grands oedèmes non-médicaux des membres inférieurs. *Bull. et mém. Soc. nat. de chir.* 53:187-195, 1927.
57. Ochsner, A., and DeBakey, M. Thrombophlebitis: the role of vasospasm in the production of the clinical manifestations. *J. A. M. A.* 114:117-124, 1940. Treatment of thrombophlebitis by novocain block of sympathetics: technique of injection. *Surgery* 5:491-497, 1939.
58. Labat, G. *Regional Anesthesia: Its technic and clinical application*. Second edition. 567 pp. Philadelphia: W. B. Saunders Co., 1928.
59. White, J. C. Diagnostic blocking of the sympathetic nerves to the extremities with procaine. *J. A. M. A.* 94:1382-1388, 1930.
60. Flothow, P. G. Diagnostic and therapeutic injection of sympathetic nerves. *Am. J. Surg.* 14:591-604, 1931.
61. Lundy, J. S. Cited by Flothow.<sup>60</sup>
62. Reichert, F. L. Interruption of sympathetic pathways for the relief of pain in the extremities. *Northwest Med.* 31:554-557, 1932.
63. de Takats, G. Surgical treatment of acute vascular occlusions. *S. Clin. North America* 22:199-220, 1942.
64. Homans, J. *Circulatory Diseases of the Extremities*. 330 pp. New York: Macmillan Co., 1939. P. 28.
65. Leriche, R., and Geisendorf, W. Résultats d'une thrombectomie précoce avec résection veineuse dans une phlébite grave des deux membres inférieurs. *Presse méd.* 47:1301, 1939.
66. Adams, J. C. Etiological factors in varicose veins of the lower extremities. *Surg., Gynec. & Obst.* 69:717-725, 1939.
67. Veal, J. R., and Hussey, H. H. The venous circulation in the lower extremities during pregnancy. *Surg., Gynec. & Obst.* 72:841-847, 1941.
68. Edwards, J. E., and Edwards, E. A. The saphenous valves in varicose veins. *Am. Heart J.* 19:338-351, 1940.
69. Edwards, E. A., and Edwards, J. E. The effect of thrombophlebitis on the venous valve. *Surg., Gynec. & Obst.* 65:310-320, 1937.
- Edwards, E. A. The orientation of venous valves in relation to body surfaces. *Anat. Rec.* 64:369-385, 1936.
70. Mahorner, H., and Ochsner, A. The modern treatment of varicose veins as indicated by the comparative tourniquet test. *Ann. Surg.* 107:927-951, 1938.
71. Pratt, G. H. Test for incompetent communicating branches in the surgical treatment of varicose veins. *J. A. M. A.* 117:100, 1941.
72. Jarjavay, L. *Contribution à l'étude du système veineux. "Les canaux de sûreté."* Paris Thesis, No. 11, 1883. 77 pp.
73. Macey, H. B. A new surgical procedure for lymphedema of the extremities: report of case. *Proc. Staff Meet., Mayo Clin.* 15:49-52, 1940.
74. Padgett, E. C. *Skin Grafting*. 147 pp. Springfield, Illinois: Charles C Thomas, 1942.
75. Homans, J. The treatment of elephantiasis of the legs. *New Eng. J. Med.* 215:1099-1104, 1936.
76. Knott, J. Gravity drainage of inflammatory edema: method for elevation of extremity. *Surgery* 5:444, 1939. The treatment of filarial elephantiasis of the leg by bandaging. *Tr. Roy. Soc. Trop. Med. & Hyg.* 32:243-252, 1938.
77. Drinker, C. K., and Yoffey, J. M. *Lymphatics, Lymph, and Lymphoid Tissue: Their physiological and clinical significance*. 406 pp. Cambridge: Harvard University Press, 1941.
78. Gillies, H., and Fraser, F. R. Treatment of lymphoedema by plastic operation: a preliminary report. *Brit. M. J.* 1:96-98, 1935.
79. Pratt, G. H., and Wright, I. S. The surgical treatment of chronic lymphedema (elephantiasis). *Surg., Gynec. & Obst.* 72:244-248, 1941.

# CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTHROPOMETER AND POST-MORTEM RECORDS AS USED  
IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

## CASE 28241

### PRESENTATION OF CASE

A fifty-three-year-old, single female office worker was admitted to the hospital because of jaundice of a month's duration.

About ten years before entry, the patient began to suffer from recurrent attacks of "indigestion," characterized by belching, epigastric distention, nausea and vomiting. These spells, which tended to occur after meals of fatty foods, continued sporadically for about six years, although the patient went on a low-fat diet, on the advice of her physician. In the three years preceding entry, she remained quite well, and gradually returned to a full diet. Two months before entry, she experienced a constant sense of pressure in the epigastrium, lasting for about two weeks. This feeling was aggravated by deep respiration and was not accompanied by any other symptom. A month before entry, the patient noted that her stools were clay colored. In the next week, generalized pruritus appeared, and the urine became deep orange yellow. She was given "vitamin K and bile salts" and was put back on a low-fat diet. The symptoms continued to progress, with the addition of weakness and lassitude. The appetite was only fair in the month preceding entry, and in this time she lost 14 pounds in weight. At no time was there nausea, vomiting, pain, chills or fever.

A younger sister of the patient had had an operation for "gall-bladder disease," and a brother had died in childhood of typhoid fever. The patient thought that she herself had had a transient attack of jaundice as a child. She denied the use of alcohol and of drugs other than those specified. Six months before entry, she had a normal menopause.

On admission, the patient appeared well developed and nourished, and in some distress from diffuse pruritus. There was evidence of recent weight loss. The skin and scleras were icteric, and all over the body there were multiple excoriations from scratching. The heart and lungs seemed normal. A smoothly rounded, slightly tender mass, approximately 5 cm. in diameter and fixed on respiration, lay in the right upper quadrant of the abdomen. The liver edge was not felt.

The blood pressure was 148 systolic, 105 diastolic. The temperature, pulse and respirations were normal.

Examination of the blood showed a red-cell count of 3,960,000 with 11.3 gm. hemoglobin, and a white-cell count of 4600 with 72 per cent polymorphonuclears, 12 per cent small lymphocytes, 12 per cent monocytes and 4 per cent eosinophils. The blood Hinton reaction was negative. The van den Bergh reaction was biphasic, with 24 mg. bilirubin per 100 cc. of serum. The hematocrit was 40 per cent. The prothrombin time was elevated to about four times normal. The serum protein was 6.2 gm., and the nonprotein nitrogen 28 mg. per 100 cc. The blood sugar was 70 mg. per 100 cc. The urine was dark amber, with a ++ test for bile pigments. The stools were clay colored, with negative reactions for bile pigment and for occult blood.

The patient was given Klotogen, Bilein and Hykinone, with a fall in the prothrombin time to normal. The temperature remained normal. On the seventh hospital day, an operation was performed.

### DIFFERENTIAL DIAGNOSIS

DR. WYMAN RICHARDSON: To summarize this case very briefly, the patient for ten years had symptoms consistent with gall-bladder disease, and then developed an obstructive jaundice and right-upper-quadrant mass. One is forced to make a diagnosis of cancer involving probably the gall bladder on the basis of pre-existing cholelithiasis. I should stop there. I shall go on, however, and add one or two things. In the first place, I had a case like this a year ago—in a fifty-three-year-old woman with a similar history—in which an indefinite right-upper-quadrant mass was disregarded because the patient was obese. I should have paid attention to it because she had a tumor of the biliary tract. In the case under discussion, the mass was definite, and I wonder if I am going to be misled about it again.

One can assume this mass to be gall bladder. One can also assume that the patient had gallstones and that she had a gallstone impacted in the cystic duct, with hydrops of the gall bladder, and another stone impacted in the common duct, with obstruction to the biliary flow. I should say parenthetically that there is no doubt that she had obstructive jaundice with complete obstruction. Of course, it is said that a palpable gall bladder is rare in the presence of common-duct stone. In other words, if this mass had been gall bladder, it would have ruled against the presence of stone. One other bit of evidence is that the mass is said to have been fixed on respiration. Ordinarily, I think

the gall bladder would tend to move on respiration. If it was gall bladder and if it was fixed, can that be taken as evidence of tumor of the gall bladder that has extended to surrounding structures and thus caused fixation? The only other evidence that I can glean from the record is the tendency to leukopenia—a rather curious blood formula for a leukopenia in that the polymorphonuclear cells were at a normal or slightly high level, the lymphocytes were decreased, and the monocytes were increased. This is not the ordinary type of leukopenia. Whether one can lean very much on that observation, I do not know. In cirrhosis of the liver, a leukopenia is common, and this might be evidence that the patient had an underlying cirrhosis. The mass felt might have been an abnormal lobe of the liver, and there might have been a tumor of the liver on the basis of underlying cirrhosis. That seems to me to be arguing quite far afield on slim evidence.

There is no mention of a palpable spleen, and in cases of cirrhosis of the liver without splenomegaly not much leukopenia is found. Occasionally, this blood formula is seen in lymphoma, more commonly with a slight increase in lymphocytes, rather than a decrease. I think that again is very slim evidence. In the patient whom I saw a year ago, the white-cell count as I remember it was between 9000 and 10,000.

I shall mention one more thing regarding the leukopenia. If there had been an impacted stone in the cystic duct, the chances are that there would tend to be some fever, presumably dependent on rather low-grade inflammation, and we might expect to have at least a slightly elevated white-cell count and slight fever.

One always ought to bear in mind the possibility at any age of toxic hepatitis, so-called "catarrhal jaundice." I remember having had a patient operated on for obstructive jaundice due to stone, I thought, who proved to have nothing but benign catarrhal jaundice. The mass that was felt in the case under discussion rather rules out this diagnosis. One would expect to feel a tender liver in a case of jaundice caused by toxic hepatitis. This mass is not spoken of as being very tender. I mention this because one should always think of it, but I cannot see any really good reason why this patient should not have been operated on for the purpose of establishing a definite diagnosis and also with the hope of being able to re-establish some form of biliary drainage, and to rule out the possibility that a stone caused this condition. With the setup as we have it, I come back to my original diagnosis: that this patient had a chronic cholecystitis and cholelithiasis and that as a result, as

sometimes happens, she developed a carcinoma of the gall bladder that extended to involve the biliary tract.

DR. JACOB LERMAN: Are you disturbed at all by the fact that the mass was smooth, if the examiner was accurate in his description?

DR. RICHARDSON: No, I do not believe I am. I am no more disturbed by his calling it smooth than I would be impressed by his calling it irregular.

DR. WILLIAM B. BREED: Nor by the fact that it did not move on respiration!

DR. RICHARDSON: That is a little more definite.

DR. BREED: Yes, but mistakes are made on that point just as often as on the other.

#### CLINICAL DIAGNOSIS

Carcinoma of head of pancreas.

#### DR. RICHARDSON'S DIAGNOSES

Chronic cholecystitis.

Cholelithiasis.

Carcinoma of gall bladder.

#### ANATOMICAL DIAGNOSES

Carcinoma of pancreas.

Cholelithiasis.

Hydrops of gall bladder.

#### PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: This patient was explored, and a huge distended gall bladder was found in which were many small stones and a large amount of colorless bile. The exploration was continued, and a firm mass was palpated in the pancreas, which was biopsied and showed carcinoma. The gall bladder itself did not show cancer. There was then a distinct problem in the surgical relief of this patient. Originally, it was believed that cholecystgastrostomy might be done, but with white bile in the gall bladder, it seemed probable that the cystic duct was obstructed and that such an operation would therefore be ineffective. Fortunately, the common duct was markedly dilated, and it was possible to anastomose the common duct successfully to the duodenum. The gall bladder was emptied of its stones and likewise drained. The patient made a fairly comfortable postoperative recovery, and the jaundice, though still present, was steadily diminishing at the time she left the hospital.

A PHYSICIAN: Was x-ray treatment given?

DR. MALLORY: I do not know. There is no mention of x-ray treatments in the record. If they are being given, I am sure it is with no enthusiasm.

## CASE 28242

## PRESENTATION OF CASE

A sixty-five-year-old Russian tailor was admitted to the hospital because of loss of weight and appetite.

The patient was in good health, except for occasional bouts of sinusitis, until about six weeks before entry, when there was gradual onset of weakness and anorexia. Constipation appeared, requiring enemas every third day. The stools were dark, but not bloody. There was no distention of the abdomen and no pain. Seven pounds in weight was lost. Ten days before entry, a local physician diagnosed "anemia," and prescribed iron and vitamin pills. No improvement followed this medication. In the week before entry, some cramping was noted in the abdomen.

The family history was irrelevant. Four years before entry, the patient had a large thrombosed hemorrhoid excised in the emergency ward of the hospital. He had also been treated for sinusitis, on two occasions, in another department of the hospital.

On admission, the patient appeared well developed, but rather undernourished. The heart was normal. The right lung field was clear, but many moist inspiratory rales were heard at the left base. The abdomen appeared full. No free fluid or masses were palpable. There was some hypogastric tenderness, but no spasm. Peristalsis was hyperactive, with high-pitched sounds. The prostate was of normal size.

The temperature was 99.5°F., the pulse 80, and the respirations 20. The blood pressure was 100 systolic, 55 diastolic.

Examination of the blood showed a white-cell count of 21,700 with 78 per cent polymorphonuclears, 9 per cent large lymphocytes, 5 per cent monocytes and no abnormal cells. The red-cell count was 4,010,000. The serum protein was 4.5 gm. per 100 cc. The chlorides were 102.5 milliequiv. per liter, and the nonprotein nitrogen 39 mg. per 100 cc.

A roentgenogram of the large bowel after a barium enema showed no evidence of obstruction. The cecum was high, and the sigmoid was rather redundant. Two diverticula projected from the descending colon. On re-examination, numerous dilated loops of small bowel were noted close to the cecum, suggesting a lesion at the ileocecal valve. Roentgenograms of the upper gastrointestinal tract showed some deformity of the duodenal cap suggestive of old duodenal ulcer. There was definite obstruction to the passage of barium by an irregular, apparently ulcerated mass in the upper jejunum. The loops of small bowel below this level appeared filled with air.

A Miller-Abbott tube was passed, and a blood transfusion was given. The temperature rose to 101.5°F., and then dropped to normal. On the third hospital day, an operation was performed.

## DIFFERENTIAL DIAGNOSIS

DR. E. PARKER HAYDEN: The history, at its outset, with a loss of weight and appetite of six weeks' duration, certainly suggests cancer. I shall exclude the possibility of cancer of the stomach simply on the failure of the X-ray Department to state that the stomach itself showed any abnormality when examined.

The onset of constipation six weeks before entry may or may not mean anything. Perhaps the patient was eating lightly or had shifted to a low-residue diet. The stools were not bloody. There was no distention of the abdomen and no pain. The serum protein was low, but the chlorides were normal. The nonprotein nitrogen was moderately elevated. The findings in the left chest may or may not be of much significance in an elderly person. The onset of definite cramps and hyperactive peristalsis indicates that the patient had mechanical obstruction on admission to the hospital, but on the other hand, the presence of some fever indicates infection — which is primary and which secondary, we must decide. The x-ray report states that there were dilated loops of small bowel close to the cecum. Whether these happened to lie close to the cecum, or actually involved the terminal ileum, is not certain. The diverticula in the descending colon, I suspect, were merely coincidental and, as so often happens, were probably not concerned in this picture.

We have evidence of an ulcerative mass in the jejunum and also evidence of obstruction near the ileocecal valve. The problem is to decide whether these findings were due to one lesion, perhaps primary at the ileocecal valve with adherence and involvement of a loop of jejunum, or whether there were two independent lesions. If there were two independent lesions, the condition might have been regional ileitis, or there might have been two independent cancers. It is difficult to be sure. Anemia and loss of weight are very common early symptoms of carcinoma of the cecum before localizing symptoms develop, and the subsequent onset of obstruction could readily have been due to involvement of the ileocecal valve with tumor. That diagnosis seems probable. The mass involving the jejunum could have been primary, or involvement secondary to a tumor in the ileocecal region. The localized loops in the region of the cecum also suggest the possibility of a herniation of small bowel through some aperture in the region of the cecum, a condition met with occasionally. However, I think I shall make a diag-

nosis of carcinoma of the cecum, at the ileocecal valve, with secondary involvement of the jejunum.

DR. RICHARD SCHATZKI: I do not know whether the record states emphatically enough that the films show no evidence of disease in the colon. The cecum is well outlined. There are several dilated loops of small intestine in the lower abdomen.

DR. HAYDEN: I was making some allowance for the fact that the roentgenogram does not always reveal lesions in the cecum.

DR. SCHATZKI: I think the fluoroscopy note, together with the films, is enough evidence against a lesion in the cecum. The upper gastrointestinal tract shows this ulcerated lesion in the first or second loop of jejunum, which has the definite appearance of malignant tumor. Some moderately but, I should say, definitely air-filled loops of small intestine are visible below this region, indicating additional involvement of the bowel below the region of ulceration. I do not see any films showing the small intestines filled with barium lower down, not because the small intestine was obstructed but apparently because such films are not here or they were not taken.

DR. HAYDEN: The loops described in the report, then, happened to be lying close to but were not concerned with the ileocecal valve.

DR. SCHATZKI: Not so far as there is evidence in the film. If there was a lesion there, it was in the small intestine.

#### CLINICAL DIAGNOSES

Intestinal obstruction.

? Lymphoma of intestine.

#### DR. HAYDEN'S DIAGNOSIS

Carcinoma of ileocecal region, with second involvement of jejunum.

#### ANATOMICAL DIAGNOSIS

Lymphosarcoma, multiple, of jejunum ileum.

#### PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: At operation, it was found that this patient had multiple tumors of small bowel. Each of these was several centimeters in length, and in each one the wall of bowel was uniformly thickened all the way around its circumference. There was ulceration of mucosa. The tumor masses were extremely friable, and in the course of exploration one of them spontaneously ruptured. It therefore became necessary to do a fairly extensive resection, and eventually received three separate segments of bowel, which contained several tumors. On microscopic examination, all showed a rather undifferentiated type of lymphosarcoma. The patient died two days after operation.

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established in 1828

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND  
PUBLISHED UNDER THE JURISDICTION OF THE  
COMMITTEE ON PUBLICATIONS

Official Organ of  
THE MASSACHUSETTS MEDICAL SOCIETY  
and  
THE NEW HAMPSHIRE MEDICAL SOCIETY

## EDITORIAL BOARD

Joseph Garland, M.D.	Stephen Rushmore, M.D.
William B. Breed, M.D.	Henry R. Viets, M.D.
George R. Minot, M.D.	Robert M. Green, M.D.
Frank H. Lahey, M.D.	Charles C. Lund, M.D.
Shields Warren, M.D.	John F. Fulton, M.D.
George L. Tobey, Jr., M.D.	A. Warren Stearns, M.D.
C. Guy Lanc, M.D.	Dwight O. Hara, M.D.
William A. Rogers, M.D.	Chester S. Keefe, M.D.

## ASSOCIATE EDITORS

Thomas H. Lanman, M.D.	Donald Munro, M.D.
Henry Jackson, Jr., M.D.	

Walter P. Bowers, M.D., EDITOR EMERITUS  
Robert N. Nye, M.D., MANAGING EDITOR  
Clara D. Davies, ASSISTANT EDITOR

SUBSCRIPTION TERMS: \$6.00 per year in advance postage paid for the United States (medical students \$3.50 per year), Canada \$7.04 per year, foreign funds \$8.52 per year for all foreign countries belonging to the Postal Union.

MATERIAL for early publication should be received not later than noon on Friday.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston, Massachusetts.

## IMMEDIATE NEED FOR MEDICAL OFFICERS

All who were present at the annual banquet of the Massachusetts Medical Society and who listened to the speeches of Dr. Frank H. Lahey and Dr. Morris Fishbein appreciate the immediate need for medical officers in the Army of the United States. This crisis was referred to also by Dr. John F. Fulton in the Shattuck Lecture, when he stated that, by the end of this year, the air forces of the Army and Navy will be expanded to include about 20,000 flight surgeons and medical officers. In other words, NOW is the time to volunteer—not six months from now, or even a month from now. Furthermore, if a sufficient number of

medical officers are not obtained by this means, there is every indication that more drastic measures will be taken to secure them.

The response in Massachusetts has been disappointingly slow, owing in a large measure to the erroneous impression of some physicians that the enrollment forms of the Procurement and Assignment Service are equivalent to applications for commission and to the fact that the information contained on these forms necessarily requires a considerable period before it can be tabulated and, hence, become available for use by the recruiting personnel of the armed forces.

To facilitate matters, as outlined in an editorial in the May 14 issue of the *Journal*, recruiting boards for medical officers have been established in all states. The office of the Massachusetts Medical Officers' Recruiting Board is located at 319 Longwood Avenue, Boston (ASP 3638). These boards, working in conjunction with the Procurement and Assignment Service, are authorized to commission directly a qualified physician in the Medical Corps of the Army, provided he is declared "available" by the state or local officers of the Procurement and Assignment Service; in such a case, the physician will be assigned to active duty within a few weeks following his application. In addition, the boards will forward applications for commissions from graduates of unapproved and foreign medical schools to the Office of the Surgeon General for individual consideration.

To repeat, the enrollment forms of the Procurement and Assignment Service are NOT applications for commissions. Furthermore, this governmental agency will NOT tell physicians what to do—whether to go, or when to go; its function consists only of acting in an advisory capacity to the armed forces and of determining whether physicians are "available" or "essential." This IS the call, and all qualified physicians in Massachusetts should IMMEDIATELY apply, through the Medical Officers' Recruiting Board, for a commission. After the war is over, let it be said that Massachusetts physicians VOLUNTEERED their services.



## INDUSTRIAL HYGIENE AND THE WAR

THE recent joint meeting in Washington, D. C., of the National Conference of Governmental Industrial Hygienists and of the Subcommittee of Industrial Health and Medicine, Health and Medical Committee, Office of Defense Health and Welfare Activities, brought out many problems that are of vital interest in the present emergency.

The five major points raised by various speakers were as follows: workers, individually and collectively, should serve as the fulcrum of all efforts to improve industrial health; the efficacy of medical, engineering and chemical controls of occupational hazards has been proved; knowledge, experience and organization are such that time-loss due to disability can be greatly reduced; threats to the health of war workers have increased, in many parts of the country, to a critical, or even desperate, stage; and to meet this emergency,—that is, to avert disaster and to establish a condition of vigorous health among all workers,—all the facilities for prevention and restoration must be expanded.

Figures released by the War Production Board showed that seven and a half million people are now employed in producing the implements of war and that double that number will be needed by the end of the year. This marked increase will intensify existing problems and will create new ones. For example, the need for medical and nursing services in small plants, which now employ about two thirds of the industrial population and which, as a rule, fail to provide such services, will be even more acute. Furthermore, the employment of women will present difficulties that require a new approach, as will the introduction of new toxic substances, and longer working hours with shorter periods of relaxation.

State industrial-health officers praised the aid furnished by the Government—both financial and otherwise—and affirmed that they had the knowledge and the spirit markedly to decrease loss of time due to disability; however, they acknowledge that they were tremendously handi-

capped by a lack of personnel—physicians, engineers, chemists and nurses.

Since the outcome of the war depends on the production of its instruments, all agencies—federal, state and industrial—must co-operate in every possible way to increase productive efficiency by improving the health of war workers. And, after the battle has been won, this service, which is the fundamental right of the millions of industrial workers in this country, should be continued.

## MEDICAL EPONYM

### PFEIFFER BACILLUS

"Vorläufige Mittheilungen über die Erreger der Influenza [Preliminary Notes on the Etiologic Agents of Influenza]" was published by Richard Friedrich Johann Pfeiffer (1858), while he was a *Privatdozent* in the Institute for Infectious Diseases at Berlin, in the *Deutsche medicinische Wochenschrift* (18:28, 1892). A portion of the translation follows:

In all the cases [31] of influenza, a distinct variety of bacillus was found in the characteristic purulent bronchial secretion. These rods were demonstrable in absolutely pure culture and usually in tremendous numbers in the cases of uncomplicated influenza. . . . The rods were found only in influenza. . . . The numbers of the bacilli kept pace with the course of the illness. . . . Numerous inoculation experiments were attempted. Positive results can be obtained only in monkeys and rabbits.

R. W. B.

## MASSACHUSETTS MEDICAL SOCIETY

### COMMITTEE ON MATERNAL WELFARE

#### CASE HISTORY: TOXEMIA FOLLOWED BY ANURIA AND DEATH

A twenty-eight-year-old primipara, when approximately thirty-five weeks pregnant, entered the hospital with marked edema, a blood pressure of 164 systolic, 92 diastolic, a trace of albumin and a sediment containing many granular and hyaline casts. She had been followed by her physician from the beginning of pregnancy and had shown no abnormalities until about the thirtieth week, when albuminuria appeared. The blood pressure was said not to have risen for another month. The past history was irrelevant; there had been no contagious diseases or any operation. The patient was treated at home for a week before she entered the hospital. Two days after admission, because of a sustained systolic blood pressure of 160 to 170

and a diminution in the urinary output, labor was induced with a Voorhees bag. The bag was expelled twenty four hours later, and an infant, presenting by the breech, extracted. The baby weighed 5 pounds, 12 ounces, and lived only a few hours. Anuria developed immediately after delivery, and the patient died forty eight hours later.

**Comment** Although the care of this patient was adequate, it was not of the most intelligent nature. If she had been hospitalized at the onset of her symptoms, and if rest in bed and a diet of  $2\frac{1}{2}$  quarts of milk a day (with absolute restriction of salt) had been instituted, improvement might have been noticed. If, under hospital care and constant surveillance, edema had increased, the blood pressure had remained stable or increased, and the urinary output had decreased, delivery might well have been considered earlier. The use of the Voorhees bag for induction warrants no criticism. It is barely possible that rupture of the membranes alone would have achieved the same end, and that if an abrupt rise in the blood pressure had occurred during the hospital stay, an immediate cesarean section might have saved the baby and lessened the degree of nephritis that resulted in anuria and death.

Some cases of anuria developing in association with hypertension and toxemia, particularly those in which separation of the placenta (which this patient did not have) occurs, have been successfully treated by decapsulation of the kidney, but this treatment is not so satisfactory when applied to this type of anuria as it is for that following incompatible blood transfusion.

## DEATH

**POPOFF**—**CONSTANTINE POPOFF, M.D.**, of Haverhill, died May 30. He was in his sixtieth year.

Born in Bulgaria, Dr. Popoff received his degree from Harvard Medical School in 1910. He was a lieutenant colonel in the United States Army Medical Reserve, and at the time of his death was awaiting orders to active service. He was a member of the New England Roentgen Ray Society and the Radiological Society of North America, and a fellow of the Massachusetts Medical Society and the American Medical Association.

He is survived by two daughters.

## WAR ACTIVITIES

### CIVILIAN DEFENSE

#### BLOOD AND PLASMA BANKS

Regulations for the administration of the Blood and Plasma Bank Program of the Medical Division of the United States Office of Civilian Defense have now been prescribed, and funds are available for grants to assist approved hospitals in establishing blood and plasma banks. Only hospitals within three hundred miles of the Atlantic Pacific and Gulf coasts are eligible for such grants. After July 1, 1942, these geographical restrictions may be modified so that grants may be made to inland hospitals. Ap-

plications should be addressed to the Chief Medical Officer, United States Office of Civilian Defense, Washington, D. C.

Technical manuals on blood and plasma banks, prepared by the Subcommittee on Blood Substitutes of the Division of Medical Sciences, National Research Council, are now available for distribution on request of any hospital to the Chief Medical Officer, Office of Civilian Defense.

The Red Cross has established eighteen donor centers in various parts of the country, which are successful in obtaining an adequate supply of blood donors for military purposes. Blood for the production of dried plasma for civilian-defense purposes will also be obtained from these sources.

Hospitals that establish their own blood and plasma banks with the financial assistance of the Office of Civilian Defense are advised to build up their reserves of blood and plasma by expanding blood collections from relatives and friends of patients who are to receive transfusions. A public campaign for volunteer donors which might compete with the work of the Red Cross should be avoided if possible. If public solicitation is necessary, hospitals should appeal to the local chapters of the American Red Cross for assistance in recruiting hospital donors. Blood donor campaigns by agencies other than the Red Cross will tend to confuse the public and may interfere with the blood collection by the Red Cross for the armed forces.

The official release dated April 17, 1942, of the Federal Security Agency and the United States Public Health Service is as follows:

Whereas on April 11, 1942, there was allotted from the 'Emergency Fund for the President' to the United States Public Health Service the amount of \$292,500, to be expended by said Public Health Service in connection with emergencies affecting the national security and defense for procuring and establishing either independently or, subject to regulations to be promulgated by the Surgeon General, by grants to public and private hospitals located not more than three hundred miles from ocean or Gulf Coast, reserves of liquid, frozen or dry blood plasma or serum albumin for the treatment of casualties resulting from enemy action, the following regulations are promulgated to govern the administration of this allotment:

#### SECTION I ELIGIBILITY FOR GRANTS

Preference shall be given to hospitals serving communities whose geographical location implies a likelihood of civilian casualties from enemy action, and which are inadequately equipped to handle such casualties.

To be eligible for a grant a public or private hospital located not more than three hundred miles from ocean or Gulf Coast (the Appropriation Act for the year 1943 may not limit grants to hospitals within this geographical area) shall

(1) Have a capacity of not less than 200 beds, exclusive of bassinets provided that two or more smaller hospitals totaling 200 beds may submit a cooperative project designating one of the participating hospitals as the grantee,

(2) Be on the approved list of the American College of Surgeons and the Hospital Register of the American Medical Association, and

(3) Have on the professional staff a physician whose qualifications are the equivalent of those

required by the American Board of Pathology for its diplomates.

## SECTION II. APPROVAL OF PLANS

A grant shall cover a period of not more than twelve months following the approval of the plan, or not beyond June 30, 1943, and may be used only for the purchase of equipment necessary for the preparation of liquid or frozen plasma, reconditioning or minor alterations of existing quarters, necessary travel and subsistence allowance of \$6.00 per diem to cover a training period, if required, of not more than one week, for the physician directing the blood-plasma project, and temporary salaries of personnel necessary for the establishment of a blood and plasma project.

The maximum grant for one hospital is \$2000.

A hospital desiring to receive a grant shall submit a plan to the Chief Medical Officer, United States Office of Civilian Defense, who is authorized to receive such plans on behalf of the Surgeon General of the United States Public Health Service. A plan shall contain the following information:

- (1) The number of hospital beds classified according to use;
- (2) The name and qualifications of the physician who will direct the plasma project;
- (3) Description of present blood and plasma project, if any;
- (4) The type and amount of plasma reserves which the institution desires to prepare;
- (5) The delivered price of equipment necessary to complete the existing facilities for preparing such plasma — such items to be numbered and described in accordance with the equipment inventory in *A Manual on Citrated Normal Human Blood Plasma*, issued by the Office of Civilian Defense, or equivalent approved substitute equipment.
- (6) The materials or labor, if any, needed for adapting existing quarters to the needs of the blood plasma project; and
- (7) The salaries, if any, to be paid additional personnel until the plasma reserve has been prepared. Salary items shall also show the proposed periods of employment for each individual and the proposed monthly rates of pay.

When a plan is recommended by the Chief Medical Officer of the Office of Civilian Defense for the approval of the Surgeon General, the hospital will be furnished a budget and acceptance form to be signed, notarized and returned to the Chief Medical Officer, Office of Civilian Defense.

## SECTION III. CONDITIONS OF GRANTS

The hospital shall agree to build up a plasma reserve of at least one unit per bed within three months after delivery of the necessary equipment. A unit of plasma is that amount derived from 500 cc. of citrated whole blood, consisting of about 250 cc. of liquid plasma.

The agreed amount of plasma reserve shall be maintained for use without charge and only for treatment of casualties caused by enemy action. The reserve shall be released for use in other local hospitals for this purpose on order of the local chief of Emergency Medical Service and for transfer within the state on order of the state chief of Emergency Medical Service,

or transfer from one state to another on the order of the regional medical officer, Office of Civilian Defense.

Liquid plasma shall be kept from being outdated by replacement of older by newer plasma. Replaced units may be utilized for current needs of the hospital in the treatment of its regular patients, provided the plasma reserve shall not be allowed to fall below the stated minimum.

All plasma shall be prepared in accordance with manuals of the Office of Civilian Defense prepared by the Subcommittee on Blood Substitutes of the National Research Council.

The hospital shall agree to continue the plasma project for its current needs after the expiration of the federal grant and to maintain for the duration of the war the minimum stated reserve; thereafter the reserve may be used by the hospital without restriction.

A record shall be kept of all blood donors, including their blood types, to expedite obtaining donors for emergencies.

No funds made available under the grant shall be used for the payment of blood donors.

Any blood plasma project under this program shall be subject to inspection by authorized representatives of the Surgeon General of the United States Public Health Service.

## SECTION IV. METHOD OF PAYMENT

Payments will be made on a reimbursement basis for expenditures made in accordance with the approved budget. Applications for reimbursement shall be notarized and addressed to the Chief Medical Officer, United States Office of Civilian Defense. The procedure for payment will be as follows:

(1) Payments from the allotment to cover the purchases of nonexpendable equipment aggregating \$300 or more will be paid upon receipt, from the authorized administrative head and accounting officer of the hospital, of an itemized statement of the purchases supported by invoices showing the date of delivery of such equipment;

(2) Payments will be made for the authorized training expenses of the physician who is to direct the blood plasma project whenever the hospital presents a notarized claim itemizing the travel and per-diem allowance incident to the training;

(3) Reimbursement for other items of the approved budget will begin only after actual production of blood plasma is started. During the first three months of production, reimbursement will be made on a monthly basis and quarterly thereafter for the duration of the grant. Such reimbursement will be made only upon receipt of a report form prescribed by the Surgeon General from the institution showing expenditures incurred during the period, total plasma prepared during the month, and the total reserve on hand to date;

(4) Payments may be withheld, and plasma produced as part of this project may be transferred by the Surgeon General, from any hospital which fails to meet the conditions of the grant or to comply with the regulations;

(5) Each hospital shall submit monthly reports during the period of the grant showing the amounts of plasma on hand and used — thereafter, for the duration of the war, the hospital shall submit such reports quarterly on its use of the plasma; and

(6) Hospitals shall submit promptly reports including clinical abstracts of any untoward experiences encountered in the use of plasma for the duration of the war

## MISCELLANY

### NOTES

The Committee on Faculty of Middlesex University has announced the appointment of Dr Ernst Mathias to the professorship of pathology in the School of Medicine, to fill the vacancy caused by the recent death of Dr Leon A. Balduf. Dr Mathias was born in Königsberg Germany and studied at the Universities of Heidelberg and Königsberg, receiving his M.D. degree from the latter in 1912. He served as a member of the Department of Pathology at the University of Königsberg and at the University of Breslau, and was decorated three times for his services in the medical corps during World War I. Returning to teaching, he became professor of pathology in the medical school of the University of Breslau, and pathologist of the Jewish Hospital in that city. He visited the United States first in 1937, when he received an honorary fellowship in pathology from Yale University. He was forced to leave Germany by the Hitler regime, came to this country permanently in 1938, and received an appointment as pathologist in hospitals at Northampton, Holyoke and Greenfield. Dr Mathias is a member of the American Association of Pathologists and Bacteriologists and of the New England Pathological Society.

Middlesex University graduated a class of eighty-six from the School of Medicine at commencement exercises held on June 1 in Waltham. Congressman Thomas H. Eliot delivered the commencement oration. Dr Stephen Rushmore, dean of the school, presented the candidates and the medical degrees were conferred by President C. Ruggles Smith.

At the annual meeting of the New England Society of Physical Medicine, held at the Ring Sanatorium and Hospital on Wednesday, June 3, the following officers were elected: Dr Arthur L. Watkins, of Boston, president; Dr Wilmot L. Marden, of Lynn, first vice-president; Dr David C. Diamore, of Boston, second vice-president; Dr William D. McFee, of Boston, secretary; Dr Howard Moore, of Boston, treasurer, and Drs Charles W. McClure and Frank B. Colloten, of Boston, counselors for three years.

## REPORTS OF MEETINGS

### EVANS MEMORIAL HOSPITAL

At an Evans Lecture at the Evans Memorial Hospital on January 23, Dr Alfred Blalock, of Baltimore, spoke on "The Pathogenesis and Physiology of Traumatic Shock."

Shock is a manifestation of vascular failure, which may be cardiac or peripheral vascular in origin. Syncope of cardiac origin, as exemplified by the Stokes-Adams syndrome or any reflex slowing, such as that caused by a sensitive carotid sinus, is characterized by bradycardia and fainting. Its onset is sudden, and its duration is short, as contrasted with cardiac collapse. The cause is myocardial trauma of any origin whether from coronary artery disease, diphtheria or tamponade. There is abrupt tachycardia. In cardiac shock, there is usually congestion of

some part of the vascular tree, either peripheral or pulmonary, in contradistinction to peripheral vascular shock. Both types may have coldness, sweating and palpitation, and an acute cardiac shock may be difficult to distinguish from peripheral vascular shock.

By definition shock is a condition in which peripheral vascular failure is brought on by a discrepancy between the existing vascular bed and the circulating blood volume which leads to tissue anoxia. Shock may result from an increase of the vascular bed or a decreased circulating volume or a combination of both. The last is probably the commonest kind. The characteristics of early shock, which is the optimum time for treatment, are hemoconcentration, rapid pulse and low blood pressure. The last manifestation is late and is not comparable with the others for early recognition. However a chart of the blood pressure over a period is the best way of evaluating the status of an established case of shock. Of 2 patients with equal blood pressure readings the one with warm extremities who has not yet called on his vasoconstrictor apparatus has a better prognosis than the one with cold extremities whose sympathetic-adrenal system has already reacted maximally.

The remainder of the discussion was concerned with secondary or hematogenic shock, in which there are vasoconstriction and an increased vascular bed. Studies reveal that immediate gross hemorrhage causing death of an animal results in none of the tissue changes considered characteristic of shock, for there is apparently no time for its development. Slow bleeding however, produces changes similar to those of shock, as evidenced by the fact that transfusion of more than the lost volume of blood after a prolonged period of lowered blood volume and blood pressure will not save the animal. The tissues become hyperemic and necrotic. Dunphy and his associates have shown by early sacrifice of animals after trauma or burns that there is no capillary damage, much loss of fluid or tissue necrosis. But shock from all causes has identical terminal tissue lesions, so that it is only by study of early cases that any differentiation can be made.

Shock may be caused by many things, but the most important are toxemia, local fluid and blood loss and nervous trauma. The reason for most of the controversy is a failure to recognize that this syndrome cannot be explained by one mechanism. Experimentally, furthermore, there is a discrepancy in terminology, method of producing shock, anesthetic used, species difference and criteria of shock. Dr Blalock employs the method of trauma using one lower extremity but imputes higher than formerly—that is at the midabdomen. In such animals, there is a local loss of fluid at or near the site of trauma amounting to half the body volume, and this is the cause of shock. The seriousness of this local fluid loss is also borne out by longer experiments on bowel handling, which allows for possible accumulation of toxic products. Here, the loss is plasma rather than whole blood. In burns 3 per cent of the body weight may be lost locally, and a similar loss in normal dogs is sufficient to cause death in twenty-five hours. This may not be the only cause but it is the most important initial one in early deaths from burns which are most numerous. Other factors, such as sepsis enter into later deaths. And since burns are causing a large percentage of deaths in the present war, the necessity of finding a satisfactory method of preventing excess local fluid loss is evident. Some form of tanning is advisable for flat surfaces.

Experimental work is being carried out on the so-called crush syndrome, but so far this has been of little practical value. However, such injuries are not rare in people

pinned for long periods under debris of bombed buildings. The main differences between the experimental animals and crushed people are the immediate changes in the former on being released in contrast with the later changes in man. In animals, those treated by pressure to the part survived in 14 out of 17 cases, whereas the control group had only 1 survival in a similar number. This was in spite of an elevated hematocrit reading and fluid loss. Therefore, treatment should consist of constant pressure to the part, with an elastoplast bandage or tourniquet to prevent excessive fluid loss in the part. Blast injuries are known to be fatal in certain cases in which no evidence of any direct trauma is present. About 40 to 50 per cent of fatalities from this cause show no signs of direct violence (Hatfield). Such persons reveal widespread pulmonary hemorrhages but not of such magnitude as to cause death by compression. In animals subjected to such forces, similar bilateral pulmonary hemorrhages are found. A blast may cause similar injuries to the brain if the head is movable, and may result in intracellular neuronal disturbances. However, such cerebral damage is considered to be an exaggerated feature by some observers.

Acute circulatory failure may be classified as hemogenic (hemorrhagic), neurogenic (spinal) or vasogenic (histamine). In the last two, the cardiac output decreases before the blood pressure, whereas in the vasoconstriction following hemorrhage and trauma to muscle, the blood pressure drops first. The degree of hemoconcentration is proportional to the loss of blood or plasma.

In the treatment of shock, adrenocortical extract is theoretically useful but does not seem to have lived up to expectations practically. A pure oxygen intake, although likewise based on good logic, has not proved practically valuable. The application of heat is advisable if the person is in the cold or has just been brought in, but the great value of heaters and blankets in the usual case seems overemphasized. Experimentally, there have been more and longer survivals of animals left relatively cold. Furthermore, there has been this same improvement in results with the local application of cold, despite the same degree of fluid loss. Granted that the amount of heat supplied was physiologically excessive, it does seem illogical to use heat, which draws blood to the part from more vital centers. When the circulating volume is therapeutically increased, the addition of heat is apparently not contraindicated. Regarding parenteral fluid administration, it was emphasized that large amounts of crystalloids not only are lost but also wash out with them large amounts of plasma protein, thus decreasing the osmotic pressure, and are, therefore, definitely deleterious. Transfusions are dangerous if incompatibilities exist, and this is another indication for the use of plasma or serum. Patients die of loss of blood volume rather than of erythrocytes.

In dangerous degrees of shock, hemoconcentration may sometimes not be found. The pulse rate is often of little value, whereas the blood pressure is a fair but late indication of shock. It is still the best gauge of response to therapy. A clinical evaluation of the situation based on the severity of the injury and the amount of blood loss is often more valuable than the blood pressure. In other words, one should not wait for changes in pulse, blood pressure or hemoconcentration before initiating shock treatment. One should never administer more than 1500 cc. of saline solution daily.

Thus, it is seen that the mechanism of certain types of shock is understood, such as the local loss of tissue fluids, but that there are many others. In general, an attempt should be made to replace the same kind of fluid as that lost. The use of whole blood is contraindicated only

when hemoconcentration is a prominent feature, as in burns. Plasma and serum are available and very useful. Cohn's albumin appears to be a hopeful blood substitute. This is a nonantigenic, hypertonic solution.

#### WILLIAM HARVEY MEDICAL SOCIETY

At a regular meeting of the William Harvey Medical Society of Tufts College Medical School at the Beth Israel Hospital on January 30, Dr. Chester S. Keefer spoke on "The Epidemiology of Hemolytic Streptococcus Infections." The early recognition that a single organism was responsible for the many diseases attributed to the hemolytic streptococcus was made difficult by the multitude of clinical manifestations, but it is now generally accepted that this is a single organism.

Hemolytic streptococcus infections account for 5 to 10 per cent of all sickness and cause about 70 per cent of infections in wartime, burns and the puerperium. In crowded communities, such as war camps, it is surpassed only by measles and epidemic influenza. It is the commonest cause of bacteremia, as well as the commonest initiating factor in acute glomerulonephritis and in recurrences of rheumatic fever. Fortunately, there has been a great improvement in treatment in the past few years with the advent of the sulfonamides.

Some advances have been made in the epidemiology of hemolytic streptococcus infections, but knowledge is still far from complete. This is especially true of the control of its spread, and methods at present are inadequate. Predisposing factors include age and season of the year. Between five and fifteen years is the commonest period for most streptococcal infections attributable to the throat, whereas puerperal fever is commonest from twenty to forty years of age. The incidence of erysipelas, on the other hand, is greatest under ten and over forty years of age. The seasonal prevalence in New England—the winter months from December to March—parallels the incidence of respiratory infections. Any wound is likely to develop some degree of infection if the normal skin barriers are interrupted. This is particularly true of burns and war wounds. Mortality rates are highest under four years of age.

The modes of spread are many. The normal habitat is largely in the throat and nose. Carriers are commonest in the winter. Infection may be transmitted by contact, hands of patients, droplets through the air and dust, and fomites in the form of clothing, food and toys. Autoinfection is not rare. Five to thirty per cent of the population are carriers of the hemolytic streptococcus, but only about a third of these harbor the significant Group A organism. The carrier state is commoner in children than adults and varies with the season, crowding, contacts and the number of respiratory infections.

Classification, as carried out by blood-agar methods, has resulted in Groups A to H, whereas in Group A there are more than twenty-eight types determined by agglutination (Griffith) and precipitation (Lancefield). The soluble products of the hemolytic streptococcus are the erythrogenic toxin, hemolysin (streptolysin), leukocidin, fibrinolysin and a spreading factor. All have been shown to be antigenic, except leukocidin, which probably is, and the spreading factor, about which little is known. The cellular components are as follows: an M substance, which is type specific and is used for the production of antiserum; a T substance, which is separable by agglutination; a C substance, which is a group-specific carbohydrate; an N.P. substance, which is a nucleoprotein and is not even species specific; and hyaluronic acid, which forms part of the cap-

sule but is not antigenic. The experienced observer can usually tell the groups from blood agar plates, but it is better to use precipitation methods with specific antisera. The type specific M substance of Group A organisms, unlike that of the pneumococcus and other organisms, is protein in character.

The most characteristic sources of Group A are human infections, of B, bovine mastitis, of C, most animal streptococcal diseases, and of D, cheese and the human body (enterococci, certain saprophytes, organisms occasionally encountered in endocarditis and Ludwig's angina). Some of the higher groups are found in pneumonia, sinusitis, agranulocytic angina, some normal human beings, milk and dogs.

There are certain well-defined phases of streptococcal infections: a toxic phase, lasting from three to seven days and causing scarlet fever and so forth, a septic phase, lasting three to seven days or longer and causing severe localized reaction and only occasional bacteremia, such as the septic sore throat, a latent phase, lasting from ten days to six weeks in which an apparently normal convalescence is marred by a recrudescence, and a late non-suppurative phase, which may last from a few days to an indeterminate length of time. The last manifestation consists of fever, lymphadenopathy, nephritis, edema, cardiac insufficiency, arthritis, splenomegaly, with hepatomegaly, and erythema nodosum. At present, there is no adequate method for preventing or protecting against this phase of the infection. There may be only a persistent low grade fever following a sore throat, and the origin may not be discovered except by the taking of an electrocardiogram. There may be edema and cardiac insufficiency without true acute glomerulonephritis, and cerebral edema, with hypermagnesemia, may occur. Convulsions may be controlled by magnesium sulfate. It is best to prevent this phase, if possible, because of the danger of permanent cerebral damage. The toxic phase may be very acute and severe, but may be controlled with large amounts of antitoxic serum. This form of therapy, however, may merely serve to relieve the toxicity temporarily while allowing septic manifestations, such as acute otitis media. In this way, the septic phase not infrequently merges into the toxic. The sulfonamides have decreased the bacteremic mortality from 75 to less than 20 per cent.

Over a period of two years in a large general hospital, 95 per cent of the streptococcal cases were caused by Group A, whereas Groups B and C were responsible for only rare human illnesses. Group B has been identified in cases of puerperal fever, endocarditis, pyelonephritis, diabetes, pneumonia, meningitis and arthritis. Of the cases studied, by far the largest number were scarlet fever (414), followed by tonsillitis (120), otitis media and mastoiditis (131), and then by a great variety of other diseases. Of the scarlet fever cases, 75 per cent were caused by five types of streptococcus, which caused 53 per cent of the other miscellaneous infections. Types 15 to 17 caused 36 per cent in the former and 22 per cent in the latter group. This prevalence of types varies with the year, community and country, but in any one outbreak in a community there is one or a small number of streptococcal types. Therefore, tracing of cases by typing is not difficult if the number is small.

In a study of multiple cases of scarlet fever in families, the same type in a family was found in 100 per cent of 10 cases and only six different types were found in all 36 cases. Therefore, spread undoubtedly occurred by actual contact. Examination of the types in streptococcal complications reveals that the same type as that of the original

focus is frequently (in 11 out of 12 cases) found in less than two weeks, whereas it is infrequently so (in 3 out of 18) after two weeks. It may be concluded, then, that later complications are largely the result of cross infection in a ward or hospital, and thus, therefore, be comes an important public health problem. Typing methods may be used to advantage in tracing cases. Strict isolation and segregation of the same types in scarlet fever and other epidemics should be carried out if at all possible or practical.

At the present time, control of infection with the hemolytic streptococcus may be approached by the isolation of the patient, the tracing of the source, and the observance of strict surgical asepsis in patients with wounds, burns and puerperal infections. At least 70 per cent of wounds and burns develop such an infection in the first week, probably from other patients, attendants, clothes and dust. The highest bacterial counts in the air occur in the morning, when beds are made and the wards cleaned, and dressings should preferably be postponed to another time.

## BOOK REVIEWS

*Handbook of Communicable Diseases* By Franklin H. Top, M.D., M.P.H., and collaborators. 8°, cloth, 682 pp., with 73 illustrations and 10 color plates. St. Louis: The C. V. Mosby Company, 1941. \$7.50.

This is a sound, up-to-date book on the diagnosis, treatment, general management and prophylaxis of all the communicable diseases, with particular attention to the public health angles involved. Anyone who needs such a book, and who does not own one, will do well in buying this. The only question that arises is, in a field already so well supplied with adequate texts, was there any real need to add another to the list? Most authors along this line are in substantial agreement, and the reviewer cannot help believing that there is small profit in rehearsing, in more or less stereotyped fashion, matters already sufficiently well covered in most libraries.

*The Proceedings of the Charaka Club* Volume X. 8°, cloth, 270 pp., with 9 plates and 34 figures. Baltimore: The Williams and Wilkins Company, 1941. \$5.00.

This volume contains a selection of papers read before the Charaka Club during the years 1937 to 1940. Of particular interest is a paper on the early years of the club, by Dr. Bernard Sachs, one of the original members. A timely publication is that of Dr. Walter R. Steiner on the experiences of a physician in the United States Sanitary Commission during the Civil War. There are twenty-one other papers, mostly representing the literary interests of physicians.

*Training and Efficiency* By E. J. J. Kl, E. H. Cluver, C. Goedvolk and T. W. De Jongh. 4°, boards, 188 pp., with 28 illustrations and 18 plates. Johannesburg, South Africa: The South African Institute for Medical Research, 1941. 10s. 6d.

This book is a study, made by the South African Institute of Medical Research, of 32 standard army recruits, presumably a fairly representative cross section of a large group of youth in that political division of the Continent. It was undertaken to determine if, by compulsory training, this class of the citizenry could not be raised to a level of efficiency that would permit of their being classified as useful members of society.

One of the results of this study was to show that this substandard condition is not the outcome of fundamental biologic defects but rather is due to environmental conditions. Primarily, the physical fitness of a large proportion of Europeans in South Africa was lamentably low, and very many of the subjects had not the initiative to overcome this condition.

It appears from the success of this experiment that there is very good reason to think that by means of compulsory physical training, supplemented by appropriate occupational instruction, the labor power of this section of society may be greatly increased and that the opinion, so often expressed, that this class is "utterly degenerated" may thus be completely refuted. As a sociologic study, the book deserves to be read, and its recommendations should be heeded.

*The Therapeutics of Internal Diseases.* Vol. IV and Vol. V. Supervising Editor: George Blumer, M.A. (Yale), M.D. Associate Editor: Albert J. Sullivan, M.D. 4°, cloth. Vol. IV, 790 pp., with 56 illustrations, 22 tables and 2 charts. Vol. V, 765 pp., with 29 illustrations, 31 tables and 1 chart. New York: D. Appleton-Century Company, Incorporated, 1941. Sold only as a set (5 vol. — \$50.00).

These two volumes complete the set, and a general index is supplied to all five volumes. Each section has been written by a man particularly interested in the system of the body under discussion. Volume IV deals with the diseases of the gastrointestinal tract, the genitourinary organs, the kidneys, the blood and the locomotor system. Volume V is concerned with diseases of the nervous system, metabolism, endocrine glands and skin, with chapters on the vitamins, allergy and chemotherapy, with sulfonamide drugs. The authors are outstanding in their respective fields, and the volumes are thoroughly sound and up to date.

The whole set can be highly recommended, for it maintains a standard rarely equaled in books of this type. Great credit should be given to the expert editing of Dr. George Blumer and his associate, Dr. Albert J. Sullivan.

*Biological Symposia: A series of volumes devoted to current symposia in the field of biology.* Edited by Jaques Cattell, Ph.D. Vol. III. *Muscle.* Edited by Wallace O. Fenn, Ph.D. 8°, cloth, 370 pp., with 15 tables and 82 figures. Lancaster, Pennsylvania: The Jaques Cattell Press, 1941. \$3.50.

The editor of this interesting volume points out that care has been taken to include an aspect of muscle physiology that has gone out of fashion in this country and has been almost totally neglected until recently. However, the rapid progress in this field in recent years justifies the hope that a reasonably complete understanding of the actual mechanism of muscle contraction is not beyond reach. The contributing authors and their topics are as follows: "Introduction to Muscle Physiology," by Wallace O. Fenn; "Muscle Function as Studied in Single Muscle Fibers," by Robert W. Ramsay and Sibyl F. Street; "Muscle and the Heart's Motto," by Frederick H. Pratt; "Muscle Excitability," by Henry A. Blair; "Action Potentials and Conduction of Excitation in Muscle," by Elil Bozler, with a discussion by A. S. Gilson, Jr.; "Conduction in Smooth Muscles," by Arturo Rosenblueth; "The Local Activity around the Skeletal Neuromuscular Junctions Produced by Nerve Impulses," by T. P. Feng; "Action Potentials of Skeletal Muscle," by Allan C. Young; "The Regulation of Energy Exchange

in Contracting Muscle," by Dugald E. S. Brown; "The Action of Muscles in the Body," by Herbert Eftman; "Changes during Muscle Contraction as Related to the Crystalline Pattern," by Ernst Fischer, with a discussion by Francis O. Schmitt; "The Significance of Oxidations for Muscular Contraction," by Otto Meyerhof; "The Efferent Innervation of Muscle," by C. A. G. Wiersma; "On the Nature of Certain Diseases of the Voluntary Muscles," by G. D. Gammon, R. L. Masland and A. M. Harvey; "Theories of Electrolyte Equilibrium in Muscle," by Robert B. Dean; "Electric Potential Changes Accompanying Neuromuscular Transmission," by J. C. Eccles, B. Katz and S. W. Kuffler. All these chapters make interesting as well as provocative reading, and no doubt every library will wish to have a copy of this volume on its shelf for reference by students and investigators in this field.

*Occupational Diseases: Diagnosis, medicolegal aspects and treatment.* By Rutherford T. Johnstone, M.D. 8°, cloth, 558 pp., with 132 illustrations and 26 tables. Philadelphia: W. B. Saunders Company, 1941. \$7.50.

This volume furnishes, in a compact form, information regarding occupational diseases. The author states that his fundamental aim is to outline a basis for the diagnosis and treatment of the commoner occupational diseases, to interpret the medical and legal phase, and to predict, from experience, the expected disability. A considerable amount of space is allocated to workmen's compensation laws in the various states and to the function of the physician as related to such compensations.

Chapters are devoted to each of the common diseases met with in industry. They are condensed to furnish valuable information, so that it is unnecessary to read a more voluminous treatise. A considerable number of case histories are given to illustrate the various diseases. The bibliography is extensive, and the book is well illustrated.

This book should be of particular value to the general practitioner.

*The Art and Science of Nutrition: A textbook on the theory and application of nutrition.* By Estelle E. Hawley, Ph.D.; and Grace Carden, B.S. 8°, cloth, 619 pp., with 140 illustrations. St. Louis: The C. V. Mosby Company, 1941. \$3.50.

The problems of nutrition are always of first importance. And if, in wartime, they are not of enhanced significance, at least they are more difficult of practical solution. What with increased food costs, rationing and, perhaps, difficulties in distribution, nutritionists are likely to find it hard to maintain adequate standards.

Sound books on nutrition will therefore be — as they should — studied with particular care. And this is a sound book. It discusses the general nutritional requirements of the body; the various food elements, qualitatively and quantitatively, that must go to maintain them; food requirements under special conditions; the diet therapy of various diseases; and lastly (in a section of more than a hundred pages), the choice, preparation and serving of foods.

It is, as most such books are, designed rather for reference than for continuous reading, and its value is enhanced by numerous charts, tables and recipes. Its weakest feature is its pictures, some of which are poorly reproduced and others seem to be of slight importance, if not actually superfluous.

(Notices on page viii)

# The New England Journal of Medicine

Copyright 1947 by the Massachusetts Medical Society

VOLUME 226

JUNE 18, 1942

NUMBER 25

## MENTAL DISORDERS ASSOCIATED WITH PREGNANCY AND THE PUERPERIUM\*

MABEL D. ORDWAY, M.D.,† AND ANNETTE M. MCINTIRE, M.D.†

BOSTON

IN an attempt to determine the existence of a psychosis due to etiologic factors found only during pregnancy, labor and the post partum period, many valuable and interesting reports of cases have been published. In 1847, James MacDonald<sup>1</sup> made a comprehensive study of puerperal insanity at Bloomingdale Hospital (now New York Hospital, Westchester Division). He included the mental disorders occurring during pregnancy, parturition and lactation, and classified his 66 cases diagnostically as mania, monomania and dementia.

C. F. MacDonald,<sup>2</sup> in 1899, recognized three distinct types of insanity occurring during the puerperal period, namely, puerperal mania, puerperal melancholia and puerperal dementia—the last, however, being rare as a primary affection.

Jones,<sup>3</sup> in an article on puerperal insanity published in 1903, used a more modern classification of these mental disorders

(1) that which occurs during pregnancy, (2) that from the date of parturition to six weeks after confinement, which we shall refer to technically as puerperal insanity, (3) insanity occurring during lactation and dating from six weeks after confinement. This classification is more convenient than accurate. Insanity is and ever will be, the product of two factors, stress and heredity.

Kilpatrick and Tiebout,<sup>4</sup> in a study of 72 cases admitted to Bloomingdale Hospital in the years 1911-1923, found that diagnostically their cases fitted under four major headings: delirium, manic-depressive psychosis, schizophrenia and psychoneurosis. As a result of this study, they concluded that childbearing apparently presents many problems of a physical and psychical nature that play a definite role in the production of psychoses. These problems of themselves, however, do not

determine the type of reaction but merely serve as exciting or precipitating agents in the onset of the illness.

In 1926, Strecker and Ebaugh<sup>5</sup> presented an article on psychoses occurring during the puerperium. In their study of 50 patients, the diagnoses reported were manic-depressive psychosis (18 cases), toxic-exhaustive psychosis (17 cases), dementia praecox (13 cases), paresis (1 case) and psychoneurosis with psychotic symptoms (1 case).

Saunders,<sup>6</sup> in 1929, reported observation on 75 women admitted to the Sheppard and Enoch Pratt Hospital who developed mental illness coincident to childbirth. This study included only of psychosis before the end of the first month after those patients who gave a history of symptoms delivery. The belief was expressed that a psychosis in the puerperal period may be an isolated experience in the life of a woman; on the other hand, there may be repeated attacks of mental illness with other children, or there may be psychoses at other times.

In 1937, Karnosh and Hope,<sup>7</sup> in their study of 231 cases selected from the records of several hospitals, concluded that the stormiest psychoses associated with childbearing develop in the period immediately after delivery, and that the only consistent or characteristic element in true post-partum psychosis is delirium, which appears in varying intensity.

Smalldon,<sup>8</sup> in 1940, in a careful study of 220 cases admitted to the New York Hospital, Westchester Division, in the years 1922-1938, gives a brief review of the changing opinion of the medical profession regarding the psychotic reaction associated with pregnancy and childbirth. He found that only about 36 per cent in the series were classified as deliriums directly attributed to the toxic-exhaustive factors of reproduction. The majority of the patients were found to have manic-depressive psychoses, the depressive type predominating. A lesser number were cases of dementia.

\*From the Clinical Research Service of the Glenside Hospital, Jamaica Plain, Boston.

†Medical Director and Superintendent, Glenside Hospital.

‡Consultant in neuropsychiatry, New England Hospital for Women and Children.



praecox, chiefly of the catatonic and paranoid types. Twenty-eight patients had psychoneuroses, and only 8 of the 220 cases were diagnosed as toxic-exhaustive psychoses. Smalldon emphasizes the difficulty of generalizing regarding the mechanisms of the reactions found in post-partum psychoses. He calls attention to a universally recognized dictum among psychiatrists that "each case of a series of post-partum illnesses must be considered as an individual, non-generalizable problem."

Linn,<sup>9</sup> in a recent study, endeavors to justify the use of the term "postpartum psychosis" as a clinical entity. He obtained his figures from several large centers as shown in his valuable contribution to the literature on this subject.

The mental disorders associated with pregnancy and childbirth appear to have little influence on maternal mortality, as shown by a study conducted by the Obstetrical Society of Boston and the Boston Department of Health.<sup>10</sup> No reference to mental disorders is found in this report.

DeLee,<sup>11</sup> who states that psychoses may begin during pregnancy or may be aggravated by it, observes that a bad heredity is found in half the cases of psychoses occurring during pregnancy and the puerperium. He also states that disturbed metabolism is commoner in women whose nervous systems are not equal to the strain of pregnancy and that, without doubt, the strain of labor is too much for many nervous systems. He believes that prolonged painful labor, without infection, explains many cases of puerperal insanity.

Some observers consider the beginning of involution of the reproductive organs and the early part of the process of lactation to have a distinct bearing on the development of puerperal psychoses.

These studies show that until about 1900 most of the textbooks on the subject made a distinction between mental disorders associated with the puerperium and those occurring apart from childbirth. For the last thirty years or more, the trend has been away from the belief that a specific psychosis occurs in the pregnant and post-partum states. The consensus among most psychiatrists is that etiologically the problems of pregnancy and childbirth do not determine any given type of psychosis.

If studies of these puerperal psychoses have little true scientific value, they do make a distinct contribution to the individual psychiatrist, the general practitioner and the specialist in obstetrics. It is to these members of the medical profession that the laity turn for advice concerning childbearing.

With increasing frequency, local physicians ask whether a woman who has had a mental breakdown following the birth of a child should be

advised against further childbearing. These, as well as other pertinent questions relating to psychoses occurring during the childbearing period, stimulated a review, and a further analysis, of the cases admitted to Glenside Hospital. In addition to the results of our own observations, we have, as noted above, turned to the published reports of other observers for additional data.

The individual patient who has recovered from a psychosis occurring post partum is deeply concerned about possible future pregnancies. Her husband is also anxious to know whether further childbearing should be avoided. They sincerely wish to avoid future mental attacks for the patient, and they wish to know the hereditary dangers for their children. They want the truth. Unfortunately, it is not possible to give a positive assurance of freedom from future mental breakdown to any inquirer.

The literature on this subject indicates that a woman who has recovered from a post-partum psychosis or a severe psychoneurosis occurring for the first time during her first pregnancy may perhaps safely become pregnant again. As in other mental disorders not associated with childbearing, the constitutional predisposition of the patient, the personality make-up and the precipitating factors are of great consequence to the physician who attempts to give even a tentative prognosis. Physicians generally regard pregnancy and childbirth as rather simple primitive biologic phenomena. According to statistics, the majority of women who bear children suffer very few complications incident to childbirth. It is rather loosely stated that only 1 in 700 to 1200 women reacts by a psychosis during pregnancy or following childbirth.

The present report is based on a study of a group of 45 patients admitted to Glenside Hospital; 43 entered during a twelve-year period, 1930-1941, inclusive; 23 patients were twenty to thirty years old, and 20 were from thirty to forty years of age when the psychosis occurred. One patient was a forty-one-year-old primipara, and another, a multipara, was forty-three years old at the time of her psychosis. The case records show that there were 27 primiparas, including a patient who was six or seven months pregnant when she was admitted to the hospital.

In the group of primiparas, 17 patients were under thirty years of age, 7 were between thirty and thirty-five, 1 was thirty-six, 1 was thirty-seven, and one was forty-one years of age. The family histories in 16 cases were said to have been negative for nervous and mental diseases; the other 3 patients had histories of manic-depressive psychosis before marriage. Of these, 1 patient had a psychotic heredity, 1 had an unstable family environ-

ment, with a definitely alcoholic sibling, and 1 had an irrelevant family history

In the multiparous group of 18 patients, the youngest was twenty three years of age, and the oldest was forty three. Only 1 patient in this group gave a history of a previous psychosis. The family history in 12 cases was negative for nervous and mental diseases.

Religion did not seem to have any particular bearing in the development of mental disorders in this group: there were 17 Protestants, 15 Roman Catholics, 10 Jewesses and 1 Greek Orthodox. In 2 cases, the religion was not stated.

Twenty seven of all the patients were reported as being mentally and physically well during pregnancy. Eighteen were emotionally upset for various reasons, such as fear and apprehension, irritability and nervousness, mental conflict about premarital pregnancy, hypochondria and poor adjustment to environmental conditions. 2 patients were mildly depressed, 1 was mentally overactive, 1 had had two babies in eighteen months, and 2 definitely did not want a baby and attempted abortion. In 1 case, the patient was worried because her husband did not want a baby. Two multiparous patients became psychotic following induced abortions (in both cases, infection followed the abortion). One of these women had experienced three normal pregnancies and believed that she and her husband could not afford a fourth child. The other had one child and could not afford to have another because her husband's earnings were very small. The former became mildly upset emotionally only in the last month of pregnancy, and the latter became depressed early.

No history or other evidence of alcoholism was found in this group. Narcotics and analgesics used preceding and during labor seemed to have no significant bearing on the development of the psychosis.

The stress of present-day life did not seem to be greater in this group than in the average American family. In several of our cases, worry over finances was given as a contributing factor to the mental breakdown. Since the majority of these patients were admitted to a hospital for nervous and mental diseases for the first time during the twelve years subsequent to the great financial crash of 1929, comparisons between this period and the preceding twelve years cannot be drawn. Worry over financial circumstances and excess of physical labor during pregnancy have doubtless always had a deleterious effect on the health of many women. Eighteen patients were considered emotionally unstable before marriage. There were no unmarried mothers, although in 2 cases pregnancy occurred

before marriage. In 7 patients, there was a definite psychopathic heredity.

Intelligence was found to be good in the majority of this group, and several patients were of superior intelligence. Thirty nine patients were

TABLE 1 Time of Onset of Mental Symptoms

ONSET	NO OF PRIMIPAROUS PATIENTS	NO OF MULTIPAROUS PATIENTS	TOTAL NO OF PATIENTS
During pregnancy	7	1	8
1 to 12 days post partum	19	8	27
13 to 21 days post partum	1	5	6
26 days post partum	0	1	1
3 months post partum	0	1	1
4 months post partum	1	1	2
Total	8	17	45

born in the United States, 1 in India, 1 in Asia Minor, 2 in Russia, 1 in Canada and 1 in Scotland. In 22 cases, one or both of the patient's parents were born in the United States.

Table 1 indicates the time of onset of the psychoses and Table 2 gives the diagnostic classifica-

TABLE 2 Types of Mental Disorder

TYPE OF PATIENT	MANIC DEPRESSIVE PSYCHOSIS	TOXIC EXHAUSTIVE PSYCHOSIS	SCIZOPHRENIA	PSYCHONEUROSIS	PSYCHOSIS WITH OTHER MENTAL DISORDERS
Multiparas	3	6	5	3	1
Primiparas	7	5	9	2	1
No specified	0	0	0	0	1
Totals	10	11	14	4	1

tions. The following case reports are brief abstracts from the records of patients who developed more or less serious mental symptoms.

#### CASE REPORTS

**CASE 3 Toxic-exhaustive psychosis.** A 25-year-old multipara had an irrelevant family history. Her previous physical health had been good. She was described as a pleasant child, normal emotional life, not easily led, a calm reserved young woman who enjoyed fine things. She graduated from high school at the age of 17, worked as a saleswoman for a few years and then married. Her first pregnancy resulted in premature delivery at 6½ months. Her second pregnancy resulted in the birth of a premature infant weighing 1½ pounds. When told of its death a few days later, she became emotionally upset and claimed that she could see her baby. Removed from the hospital to her home on the 10th day, she rapidly developed somatic complaints, suffered from insomnia and was somewhat violent. There were visual hallucinations, feelings of unreality, many somatic complaints and periods of confusion. At the time of admission to Glenside Hospital there was a pronounced secondary anemia. Although there was some improvement in her condition the patient was taken home against medical advice after about 5 weeks of hospital care. There was no evidence of syphilitic infection to account for her inability to carry her babies to full term. The patient was readmitted to this hospital

a few years later suffering from insomnia, and it was believed that she was hallucinated. According to her husband, she had made a good recovery from her previous psychosis within a few weeks and then seemed quite normal. But she constantly looked forward to having children and brooded a good deal over her deceased infant. She was again taken to her home against medical advice at the end of 5 weeks. The second psychosis in this case was diagnosed as a catatonic type of schizophrenia.

**CASE 4. Manic-depressive psychosis: manic type.** A 27-year-old primipara with a definitely psychotic heredity and an intelligence above average, at the age of 17 had a manic-depressive psychosis, manic type. On recovery from this illness, she entered a normal school, graduated, and taught school. She was married at 22. Except for the poor heredity and the fact that a psychosis developed about 10 days post partum, her "nervousness and irritability" shown at times throughout her pregnancy would not have been notable. She went through a fairly typical manic episode, which lasted for about 3 months.

**CASE 5. Manic-depressive psychosis: depressive type.** A 39-year-old, well-educated multipara had had no previous mental attacks. The family history was irrelevant. Her last child was born  $3\frac{1}{2}$  months before she was admitted to Glenside Hospital. Physical examination revealed a lacerated cervix; otherwise, the general physical condition was good. This patient was "much depressed before, during and subsequent to confinement." Catamenia had returned before we saw her, and "were too frequent, too profuse, and of too long duration during her hospitalization of 4 months and 10 days." There were some delusions of a mild paranoid type. Mental improvement is recorded as "gradual and uninterrupted."

**CASE 10. Psychoneurosis.** This patient was 35 years old when she married the man by whom she had become pregnant. Her anxiety state dated from the time she was certain of her pregnancy. She had always been reluctant to marry because she had an excellent position and enjoyed working. She was described as gay, sociable, high strung and self willed. She enjoyed dancing, and had many friends. There was a strong mother attachment. She got along very well during the first 3 months of pregnancy, and then became depressed and agitated, brooded over having a child, and was fearful. No psychotic symptoms were present during the 30 days the patient was at Glenside Hospital. Improvement was gradual. She gained some insight and became interested, alert and cheerful.

**CASE 17. Toxic-exhaustive psychosis.** A 25-year-old primipara had been married 18 months when her baby was born. Her marital life was "congenial and happy." Her previous health had been good. She was temperamentally cheerful and lively. The family history was irrelevant. During her pregnancy, the patient was "wonderfully well." She was delivered at a hospital. There were no complications. She remained in the hospital for 10 days, did not sleep well, became apprehensive, and heard comments that disturbed her. The patient was transferred to a hospital for mental diseases for a period of observation. On the 20th day post partum, she was admitted to Glenside Hospital. She was confused, disoriented, overtalkative and destructive but not assaultive; there developed a feeling of unreality about her husband and her mother. Later, the patient admitted vague auditory hallucinations. The blood pressure, temperature and laboratory findings remained normal. She was hospitalized for  $4\frac{1}{2}$  months and made a good recovery.

**CASE 19. Psychoneurosis.** A 35-year-old multipara, predisposed to emotional upsets, had had hysterical episodes brought on by frustration 7 years previously. She had always had difficulty in adjusting herself to environmental changes. There was a history of asthmatic attacks for many years. Her mother was psychotic. The patient was said to be very industrious, with an intelligence above the average. She was married when 25 years old. Her first child was 10 and the second (an unwanted baby) was 1 year old. The patient "had not been well since the beginning of her last pregnancy." She was discouraged because she had not thought she would become pregnant again. She tried to abort, without success. After the baby came, she was restless and nervous, her asthma grew worse, she was depressed and tearful, shunned social contacts, "felt nervous" and tried to run away. She remained at Glenside Hospital 30 days and seemed to respond favorably to psychotherapeutic treatment. She was not well enough to go home, but left the hospital against advice.

**CASE 22. Manic-depressive psychosis: depressive type.** A 46-year-old multipara was admitted to Glenside Hospital suffering with a manic-depressive psychosis. This was her second attack. Her case is recorded here because during her first pregnancy she was "overactive and flighty." This mental state continued until after the death of her baby, when it was 7 months old. Two months later, her mother died, and the patient went into a depressed state that lasted several months. There were two subsequent pregnancies, with delivery at term without incident. The family history was negative so far as known to the informants.

**CASE 26. Toxic-exhaustive psychosis.** A 29-year-old primipara whose previous health had been "good" had been married about a year. One sibling had been a patient at a hospital for mental diseases. Previous to delivery, physical examination revealed a loud, blowing systolic murmur, apparently of rheumatic origin. The patient developed mental symptoms soon after childbirth, and was admitted to Glenside Hospital when her baby was 2 weeks old. At first, she was fearful of insanity. At times, she had both auditory and visual hallucinations. Later, she was confused, disoriented, extremely agitated, excited, fearful, suicidal and homicidal. She developed local abscesses and ran a septic temperature for several weeks. At the end of a month, improvement began and was progressive and continuous until she went home "on visit." The duration of the psychosis was 3 months.

## DISCUSSION

Emotional instability is commonly found in women during the period of pregnancy. It is not, however, necessarily caused by this state. Many of our patients, and members of their families as well, assured us that their general health during this period seemed to be better than at other times. It is highly improbable that pregnancy in itself, in a previously healthy woman, may be considered a true etiologic factor in the psychoses of pregnancy and the puerperium.

It is true that sociologic and economic factors complicate the clinical picture of pregnancy and childbirth. Inherited (constitutional) tendencies and the personality make-up of the patient are

important contributory conditions. No two persons react in the same way to the ordinary stresses of life, and individual personality trends and problems may act as predisposing factors in any mental breakdown. It is essential to study the patient as a person quite apart from her specific symptoms. Marriage calls for adaptation to a new experience. Childbearing makes more new demands on the woman, and these demands often come before she has successfully adapted herself to the personality of her husband and to the new environment confronting both of them. Maladaptation usually indicates considerable emotional conflict, which alone may produce a so-called "nervous breakdown." Feelings of guilt often result from the use of contraceptive measures, and such feelings may be of serious import when abortions have been induced or attempted, or in an extremely psychoneurotic woman.

This series of 45 cases indicates that as contributing or precipitating factors pregnancy and labor play a significant part in the psychosis occurring within three weeks after delivery and also in many cases in which the psychosis develops somewhat later. Only 2 patients in this series became psychotic as late as four months after delivery.

So far as symptomatology and prognosis are concerned, the fundamental symptoms manifested in the psychoses under consideration do not seem to differ from those of the other biogenic psychoses. Pregnancy and parturition are emotional as well as physical experiences. In an article bearing on experience as a psychiatric concept, Kahn and Cohen<sup>12</sup> state:

Every individual has a *capacity to experience* which is peculiar to him. That many individuals share similar experiences is quite possible; that all individuals have the same experiences is impossible. For, each individual brings into the world *his* capacity to experience, and each individual differs from every other individual in that all his capacities, necessarily including his capacity to experience, have been derived fundamentally from the biological potentialities which he has inherited from his progenitors.

We feel justified on the basis of experience in accepting the fairly well-demonstrated postulate that individual biogenic weakness, although the resistance to environmental conditions may be only temporarily lowered, underlies all the biogenic psychoses. This study does not show that toxic-exhaustive factors, which are apparently the result of pregnancy and childbirth, produce symptoms that are different from those accompanying other toxic-exhaustive psychoses. Psychologic stresses, and the varying reactions of the patient

to them, are of the same relative importance here as in the other biogenic and psychogenic psychoses. In many other types of mental disorder occurring in adult life, one may find a history of long-continued economic stress given as a contributing cause. And unquestionably this type of strain in itself produces a profound anxiety state in the woman who is about to bring a child into the world. Other situational factors—such as incompatibility between husband and wife, an undesired pregnancy, a definitely unwanted child, a feeling of inadequacy about assuming the responsibilities of motherhood, and a previously sheltered life without having achieved emancipation from her own protective mother or father—are noted as contributing factors. One or more of these conditions recurred often in the 45 cases here considered.

### CONCLUSIONS

Mental disorders associated with pregnancy and the puerperium as reported by many observers may easily fall under the usual familiar nosologic headings. Many observers have found nothing specific in psychoses occurring post partum. However, as contributing and often as precipitating factors, these two incidents in a woman's life should not be disregarded.

The term "puerperal insanity" will doubtless fall into disuse, and a better term will be substituted. At present, it seems to be commonly used only in a descriptive sense.

Owing to emotional and functional alterations during pregnancy and the puerperium, many women are, by reason of poor heredity, unable to go through the long period of gestation without a break in mental and emotional integrity during the puerperium.

Endocrine and metabolic imbalances may play a large part in these and other psychoses. Evidence of their etiologic significance is insufficient for any more definite statement to be recorded.

The great need for early educational preparation for parenthood for both sexes cannot be too often emphasized, or too often stated in nonmedical as well as medical literature.

Prenatal care, including, when indicated, psychiatric study and psychotherapy of a re-educational character, should be readily available to every pregnant woman, no matter what her social and economic status.

### REFERENCES

- 1 Macdonald, J. Puerperal insanity. *Am. J. Insanity* 4:113-163, 1847
- 2 Macdonald, G. F. Puerperal insanity—a cursory view for the general practitioner. *Med. Rec.* 55:235-236, 1899
- 3 Jones, R. Puerperal insanity. *Am. J. Insanity* 59:601-620, 1903.

4. Kilpatrick, E., and Tiebout, H. M. A study of psychoses occurring in relation to childbirth. *Am. J. Psychiat.* 6:145-159, 1926.
5. Strecker, E. A., and Ebaugh, F. G. Psychoses occurring during the puerperium. *Arch. Neurol. & Psychiat.* 15:239-252, 1926.
6. Saunders, E. B. Association of psychoses with the puerperium. *Am. J. Psychiat.* 8:669-680, 1929.
7. Karnosh, L. J., and Hope, J. M. Puerperal psychoses and their sequelae. *Am. J. Psychiat.* 94:537-550, 1937.
8. Smalldon, J. L. A survey of mental illness associated with pregnancy and childbirth. *Am. J. Psychiat.* 97:80-101, 1940.
9. Linn, L. The psychoses of pregnancy. *Dis. Nerv. System* 2:280-285, 1941.
10. Maternal mortality in Boston for the years 1933, 1934 and 1935: a study conducted by the Obstetrical Society of Boston and the Boston Department of Health. *New Eng. J. Med.* 216:43-51, 1937. Editorial: Maternal mortality in Boston. *Ibid.* 218:71, 1937.
11. DeLee, J. B. *Principles and Practice of Obstetrics*. Seventh edition. 1211 pp. Philadelphia: W. B. Saunders Company, 1938. P. 377.
12. Kahn, E., and Cohen, L. H. The way of experiencing as a psychiatric concept. *Psychological Monographs* 47 (No. 2): 381-389, 1936.

## PRESIDENTIAL ADDRESS\*

CHARLES H. DOLLOFF, M.D.†

CONCORD, NEW HAMPSHIRE

**I** VIEW my task this evening as definite and inescapable. I must give a presidential address, saying words and expressing thoughts befitting a time-honored anniversary, yet finding myself without the wisdom and special ability the occasion calls for. Not of the same mold as most of you, with an experience and training of quite another sort, I have from my medical cradle been nurtured in a cloistered life that scarcely fits me for a real understanding of the things that are of interest and concern to you in the private practice of medicine, and I frankly confess to being considerably confused and uncertain of the form and substance this address should take.

Had I followed the example of my illustrious predecessor (and, whom better could one pattern after?), I would, without more ado, have prepared a paper for the afternoon session. But since a president's paper, being *ex cathedra*, is not open to discussion or even question as to its validity or scientific integrity, I hesitated. Ez Jones, of course, would have no need for any such hesitation.

Therefore, it has seemed best to say whatever I have to say, here at this banquet where the warmth and encouragement in these many feminine eyes will serve to dilute and weaken what otherwise would have been just the concentrated essence of a cold stare from a roomful of scientifically critical conferees.

Had I elected to read a paper this afternoon, being mindful of the old admonition that "the shoemaker should stick to his last," I believe I would have said something about that very much misunderstood and therefore quite unhappy branch of medicine known as psychiatry. And, mark you, at the very onset I would have boldly insisted that psychiatry must now be recognized as an important aspect of general medicine, as well as a weird specialty, in spite of the woman who said to one of my kind, "If you were only a physician instead

of a psychiatrist I should like you to take my husband's blood pressure," and in spite of the man who commiseratively said to me, "Now if you were only one of them M.D.'s you could probably get some new tires."

Psychiatry is an aspect of general medicine because mental and emotional factors play such a significant role in invalidism. More and more are we being oriented to the concept that there is a definite relation between physical and mental disorders. More and more is the value of treating the total personality, the patient as well as his disease, being better appreciated.

Thus, the true function of medicine must be the study and treatment of man, himself, as well as his organs and cells, if the practice of medicine is to be kept very much above the level of a glorified veterinary science, and I dare say even a horse doctor would admit that if he could only tell what was on the horse's mind he could the better treat the horse's belly.

From the practical standpoint of treatment, however, it is still quite useful to consider the individual not as one person but as two,—a physical man and a mental man,—the treatment required varying according to which man it is, provided, of course, we bear in mind that it may be both.

Therefore, in our conquest of disease we should, to use a modern idea, wage a total war. Yet how can physicians wage total war when lawyers get so much in the way? How can we wage total war against pathologic drunkenness, for example, when the legal dictum is that a man may drink himself into the grave and his family into destitution unless he can be certified as "insane," generally a difficult thing to do because incompetency, the legal test, is rarely manifest? And how can we wage total war against mental disease in general when the law hinders early treatment by making certification necessary for admission to a remedial hospital, branding the mild or recent case with the word "insane," with all the unfortunate consequences that flow therefrom? Lawyers are naturally concerned with arranging for the protection

\*Presented at the annual meeting of the New Hampshire Medical Society, Manchester, May 13, 1942.

†Superintendent, New Hampshire State Hospital, Concord.



around which there still rages much controversy but whatever one's opinion about the Freudian theories and technic, it must now be conceded that from being static, psychiatry has become dynamic, from being chiefly descriptive, it has now become interpretive, and from treatment en masse, it is now recognized that each patient is an exquisitely individual problem.

In this war that engulfs us, there is more need than ever before for psychiatry's contribution. Those mentally unfitted for army service must be eliminated. Civilian morale must be maintained. So loosely, so ambiguously, has the term "morale" been used that it has almost lost its meaning. Real morale is built neither by slogans, catch phrases, song and dance acts nor even by movie actresses on whirlwind visits through army camps. At best, this is only diversion and has little to do with basic principles. If you would know morale, observe the Russian people and the Russian army. Obviously, they are a people who believe very deeply in the things for which they are fighting. It is their faith in themselves and their institutions that is sustaining them. There are no slogans, dances or even hostesses in the Russian camps. May we too learn how to sustain ourselves through the weariness of continuing frustration! There is work, sacrifice and responsibility for everyone. Not a vestige of the world we have dimly anticipated for those who follow will continue if we fail each other.

I spoke in the beginning of my feelings of inadequacy for meeting the challenge of this occasion, but it is clear to me now that it should not be difficult to pay tribute to the strength and harmony of this venerable society.

One of my duties this year was to send a letter of felicitation to the Connecticut Medical Society on the celebration of its sesquicentennial. I wrote:

The New Hampshire Medical Society congratulates the Connecticut State Medical Society on the approaching one hundred and fiftieth anniversary of its founding. We recall the pleasurable satisfaction we experienced at our sesquicentennial way back in 1941. Connecticut did well to emulate New Hampshire a century and a half ago in forming a state medical society and in profiting from the longer experience of the older brother in the right way to maintain the vitality necessary for a long life. If you again emulate New Hampshire in the form of celebration you deem worthy of such a notable event, you will make it a festival such as will give your founding fathers at least one very restless night.

I tell you this because in the first place you are entitled to know what kind of rascally advice your president gave to our neighbor, and secondly because it is pleasant to recall and relive for the moment the very happy celebration of a year ago. To be sure, it was quite a let-down for an august and dignified society such as ours, but very helpful and mentally healthful, if indulged in only once in a hundred years, more or less.

One hundred and fifty years is indeed a long life, and there must have been some need in the hearts and minds of the members of this society to explain its prolonged virility through many social and economic stresses.

The most valuable purpose of such an organization as ours is the improvement of its members by advance in knowledge. No class stands in greater need of getting together frequently. You are called on to decide complicated problems involving the well-being, the very lives, of your fellows. The experience and knowledge of even the most learned is limited, and it is easy to become rusty. There is no corrective equal to discussion with others.

To be sure, much of what has been said here during the past two days will be published in the *Transactions*, but the man deceives himself who fancies he can derive the same benefit from reading the transactions as he would from attending the meetings, for he misses the second great object to be obtained in a society like this—the binding of its members together by friendly association and personal acquaintance. More than ever, in these dark and tragic days, do we need the trust and friendship of each other.

I still view with astonishment my election to this presidency. I was deeply touched by the honor and shall always think of it as an index of your democracy.

However, beyond this one election, I do not see that your habits are much akin to those of our great American democracy, for although fate has made me a war president, it does not escape my observation that you have no apprehension about "swapping horses while crossing a stream." I salute the new horse and assure him the load is not heavy. There are draft horses to do the work.

Finally, in surrendering the gavel, I can at the moment think of only one thing nicer than being your president and that is being welcomed into that charming coterie of aging men—your ex-presidents.

# THE NEUROLOGIC ASPECTS OF DEFECTS IN SPEECH AND READING

EDWIN M. COLE, M.D.\*

BOSTON

MUCH of man's success depends on the use of words. There is surprisingly little interest on the part of the medical profession in how people use words. Some time ago, I thought it would be of value to establish a clinic to study patients and their use of language. "Language" has many connotations, and perhaps a better term would be "wording," which means how words are produced in spoken and written form, and how they are received by ear and eye. This study has been the function of the Language Clinic at the Massachusetts General Hospital.

Of the patients who come to the clinic for study, the youngest group and one of the largest groups is that of children of three and a half, four and five years of age who do not talk or do not talk in an understandable way. These children usually appear two or three weeks before the opening of school, when worried mothers bring them in saying, "Johnny doesn't talk yet, and he'll have to learn before Labor Day when he goes to school." Or else the worried parent who has waited still longer brings the child in during October with the sad tale that the child has been rejected from school because he could not talk or because his speech was not understandable. Sometimes, parents are worried earlier, and the children are seen before they are ready for school. Such parents are usually apprehensive about the child's intelligence, for intelligence and ability in wording are synonymous to many. This, of course, is not true.

In the study of this group of poor talkers, the late talkers and poor talkers can be divided into several groups. In the first place, there are some who do not talk apparently because of poor intelligence. Such a patient, a little boy of seven, was brought to the hospital recently. He had for the second time been rejected from the first grade because his speech could not be understood and also because he could not fit into the group situation at school. The teacher thought that his lack of development in talking made it impossible for him to fit in with the other children. So far as could be ascertained, the child had no physical defects as judged by an examination of his sensory-motor system and his general health. He had had but little illness. His speech was quite difficult to understand. He used many words that could be understood only by his mother, who was adept

at interpreting them. A careful psychometric examination was made, nonlinguistic tests being used, and the child's mental age was found to be far below his chronologic age; in fact, it was only a little above three years of age. In such a case, then, in the absence of other causative factors, it is fair to say that poor intelligence, as measured by suitable intelligence tests, is the cause of poor wording. This is not always so, for children with very low mental ages sometimes manage to talk quite well.

Another subgroup of late and poor talkers includes children with deficient hearing. These children are puzzling, for they hear some sounds, and hence the fact that they are partially deaf escapes many observers, including their parents. They may like to listen to the radio, and they may jump when a dog barks or a bell rings, so that obviously they are not deaf. As a matter of fact, they often respond to commands, and the mother quite rightly says that they understand what is said and, therefore, they must have hearing. Careful evaluation of these cases, however, may show that a good deal of hearing has been lost. Some of these children have a loss of hearing in the high frequency range. This is a selective type of deafness, excluding many of the consonant sounds, such as *s*, *sh*, *t*, *th*, *f*, *v* and a few others, from the child's hearing. Such children are unable to reproduce the speech that they do not hear. Their speech is quite unintelligible, for it is without so many of the sounds one is accustomed to hear. Some of these patients have a selective or high-frequency type of deafness; others are slightly deaf in all ranges of frequency. There are a good many such cases; certainly, there are enough to make one realize the advantage of having a painstaking evaluation of a child's hearing done by a competent otologist before any other therapy is begun. Hearing aids in these cases may be of great assistance, and other measures may improve the child's speech.

There is a third subgroup of nontalking children. This, in my experience, is a small one. It consists of children who seem to hear sounds but do not associate meaning with words. They have been described in the literature as "word deaf." Such children obviously do not respond to their parents' words, and are usually very much interested in movements, expression of faces and all the other meaningful signs they can observe.

\*At present in leave of absence from Harvard Medical School. Head of the Linguistic Clinic and assistant in neurology, Massachusetts General Hospital.



Most children, however, who do not talk well or do not talk at all at the expected ages seem to have no physical or mental defects; that is, their intelligence is average or better, their hearing is adequate, they show no physical defect of the organs of speech, and there is no evidence of brain or nervous-system disease. Yet they talk late, or, when they talk, use poor speech, which may be described as very marked baby talk. This group, which is large and in which there is no demonstrable defect, is a particularly challenging one, which I wish to call "motor speech delay."

Second to these children who do not talk well at the proper time come the group who talk with a stutter. I use the terms "stuttering" and "stammering" interchangeably, for there is no difference in the underlying processes. Some persons have difficulty because of repeating one sound over and over again; others, who cannot get a single sound out, have what is known as a "block type" of stutter. These disturbances may be so severe as to be tremendous handicaps, or they may be so slight as to escape observation. The hemming and hawing of many speakers is a form of this same thing. One usually sees little children about to start school, or who have just started school, who stutter. Their parents quite rightly feel that the handicap may be disturbing to school progress, and hence the patients are brought in for help. Frequently, the stutterer is an adolescent whose career in school has been a difficult one because of his speech defect. At adolescence, he wishes to develop a more useful personality and, to this end, to eradicate his speech defect. Stutterers who present themselves for help consequently range in age from early childhood through the growing years. One can find among them only one common denominator—the fact that they stutter. Their organs of speech and neurologic control vary as among other persons; there is no commonly found physical defect to explain the stuttering. Stutterers, then, are a group gathered together because of their symptom.

There are, of course, large numbers of children who come in to the Language Clinic because of organic defects interfering with speaking. In enumerating such defects, faulty alignment of the teeth should be mentioned first. I hasten to add that it is surprising how well children can talk with very poorly aligned teeth, and it is only rarely that the teeth are the cause of poor speech. Cleft palate is another organic defect conditioning speech. The operative repair of cleft palate is now so well performed that it is a pity that more patients do not talk better after the operation. That they do not, in my opinion, is because of inadequate postoperative training. If a child is given an altered equipment for the production of

speech, he must be taught properly how to use it, for he still has in his memory, as correct speech, the sounds so poorly enunciated with his cleft palate. As the operative age becomes lower and lower, this hazard becomes less and less, but even so, the soft palate needs to be stretched and used properly if good speech is to result. Among organic defects influencing speech, deafness should be referred to again. Suffice it to say that many children apparently deaf since very early childhood escape notice until they reach the upper grades in school. Finally, there is the large group of organic defects whose lesion is in the nervous system as a result of cerebral birth injury. Many of these children have poorly co-ordinated movements or spastic movements, all of which are reflected in their speaking. In some of these cases, particularly when there seems to be good intelligence, some improvement in talking can be gained with good speech training.

An interesting group in the clinic might be classified as suffering from misuse of the voice. These are children whose speech is defective because, along the line of their development, they misused their voices for one reason or another. In little children, the misuse sometimes follows tonsillectomy when, owing to a sore throat, the child splints his soft palate for a prolonged period, and then develops the habit of talking with a good deal of hypernasality. His speech sounds almost as though he had a cleft palate, and the defect dates from the time of the tonsillectomy. This defect is the child's response to a painful throat, and can readily be overcome soon after the operation by proper throat exercises before the restriction of voice becomes fixed. At puberty, not infrequently, boys misuse their voices and report with a speech disturbance as a result. An example of such a patient was a boy of thirteen, rather small for his age, whose mother brought him in because of his high squeaky voice, which could hardly be heard. He had developed this voice during the six months preceding his hospitalization. On examination, it was found, when he was asked to make certain sounds, that he had a very good, unusually deep bass voice. When questioned about this, the patient rather shamefacedly admitted that he did have this sort of voice but he was embarrassed by it because it seemed so deep and large for a small fellow. He had developed a falsetto speech to save himself embarrassment. Another somewhat similar case is that of a young man of thirty-five who came in with an excessively husky voice. He had been carefully examined in the Throat Clinic, and no abnormality to which the voice could be ascribed had been found. On examination, it was found that this patient had sung in a boys' choir. He had had a very fine soprano voice. During pu-

berty, he continued his work in the choir and found that with some effort he could continue the soprano parts with which he had been so successful. Some time later, he became a singer with a jazz orchestra and was popular because of his lovely, high, crooning voice. It was after using his voice in this way for quite some time that he found it increasingly difficult to speak above a husky whisper. When he was seen in the clinic, he could still raise his voice to a high soprano falsetto tone for singing, but his voice for speaking seemed to have suffered as a consequence.

Another large group of patients seen in the Language Clinic are those who have lost the ability to use language. These are the cases of aphasia not infrequently seen in hospital and general medical practice. Aphasia is by no means limited to aged people who have had shocks, associated with hemiplegia. A good many of these patients are young people who have had vascular accidents or other trauma to the brain and who apparently have years of life ahead of them. A study of aphasia helps one to gain an understanding of the language processes. The patients who lose ability in wording may have a defect chiefly in their ability to say words. Another group of aphasic patients show their greatest defect in ability to read print. They become relatively alexic. Finally, a third group show their greatest defect in ability to understand the spoken word. I do not believe that any one of these parts of the language processes can be affected without causing a defect in the other parts as well. However, the proportion of one defect in relation to the others is a major factor. By evaluating this factor carefully, one learns much that is of great neurologic value regarding the cerebral localization of the lesion causing the aphasia. One also learns that there is an interrelation between the different areas of the brain involved in the language processes. Thus, when the lesion is in the motor speech area in the frontal lobe, talking may be completely lost, where as understanding of words and of print is only partially lost. This interrelation is of particular consequence from the therapeutic point of view. In planning retraining exercises for the patient who is aphasic, one can do much by working through the spheres of language relatively intact, to improve the portion of language most affected. A recognition of this fact also points the way for help in other language problems without recognizing the abnormality. Thus, one can remedy the speech defect by working through the auditory and visual speech areas, that is, through the hearing of words and the reading of print. Similarly, the reading disability is remediable by the backing of poor performance in this one language

process with better performance with the spoken word.

With these facts in mind, it may be readily recognized that no satisfactory work with disorders in wording can be carried on without a thorough study of aphasia. In the sphere of language, as elsewhere in the study of man's biologic processes, knowledge of function is increased by the observation of changes associated with disease.

I have described, then, various groups of patients whose chief difficulty is their output of words. Another large group are examined because of difficulty in school. These children may be regarded as having a learning difficulty. It is self-evident that a child's learning in school is by means of his wording. Facts and school experiences come through his ears as the spoken word, and through his eyes as the printed word. He expresses his thoughts and thereby gains experience, his knowledge being measured by his teachers through more wording, his speech and his written productions. Since wording is the medium by which learning in school is accomplished, learning difficulties frequently resolve themselves into difficulties in wording. The implications of this fact are tremendous and are generally overlooked.

In considering a child's learning difficulty, one of course investigates his general health, which may be a retarding factor, and his physical equipment, particularly his sense organs and his general motor equipment. Further investigation leads to attempts to evaluate the child's intelligence. There are numerous forms of psychometric examinations, all of which evaluate intelligence merely in terms of the given test. Many of these tests are given through the medium of wording, and since many of the children investigated are deficient in this respect, the limitation in language rather than one in intelligence is frequently measured. I know of no test that is foolproof in this respect. Of course, the most unreliable for this purpose are group intelligence tests which require successful use of language before the test can be mastered. Individual intelligence assays, then, must be employed. Even these lean quite heavily on oral directions, and some of them on printed material. Moreover, since they presuppose considerable experience in language, many of these patients, who are deficient in language skill, are at a disadvantage. The most helpful means of evaluating intelligence for this purpose has been to use a fairly large battery of tests, some of which depend almost entirely on performance. When this is done, one usually gains a reliable idea of the child's academic potentialities from the point of view of his intelligence.

One inevitably sees children whose defect is discernible by means of a careful psychometric examination. Such children are described as having a somewhat retarded intelligence, and in some cases this seems to be the explanation of their performance. There are many more, however, who in terms of mental tests have adequate intelligence and whose scholastic achievement is far below what might be expected of them, in view of their chronologic and mental age, and even in view of their grade placement. The so-called, mythical "average child" of eleven years having an average intelligence quotient of 100 should have a mental age corresponding to his chronologic age, and on the basis of average public-school performance, he should be entering the fifth grade in school; theoretically, his performance in arithmetic, reading and spelling, to mention only the fundamental subjects, should be the average for children beginning fifth grade. Of course, such an average child does not exist, and one finds wide variations from this norm. Thus, I have already described the child whose variation seems to be one of retardation in the mental age, accounting for retardation in scholastic achievement and possibly in grade placement. However, some of these children have a mental age that is average or much better than average for their chronologic age, and their performance in school lags well behind what would be expected of their mental age. This inconsistency must be explained. In the absence of physical and mental defects, one must look further for an explanation. When such a child's academic achievement is measured, his performance in arithmetic is generally far superior to his performance in reading and in spelling. When the use of words, printed and written, is concerned, the child's greatest failure is apparent. Here, then, are retarded children whose problem is not so much learning per se as it is the difficulty in wording, particularly in reading, writing and spelling. These cases have been described by others as congenital reading disabilities.

\* \* \*

In this study of cases seen in a clinic devoted to language problems, the difficulty of some patients is explainable on the grounds of organic defect. Others show no organic defects, and yet their wording is defective. Among them, I have described those who acquire the ability to talk late and who talk poorly; one recognizes little children of three, four and five having a motor speech

delay. Then, there are the large group of stutterers, ranging from the very severe stutterers to those whose residual defect is only a slight hesitation in speech. On the auditory side, there are those who do not seem to understand words and hence have difficulty in reproducing them. These are cases of central-type or word deafness. Finally, there are the large group of reading disabilities.

These patients have a common denominator—their heredity. One finds, when investigating the heredity of any one of these types of cases showing difficulty in wording, that in the family there are cases of right-brainedness as well as the usual left-brainedness. By this, I mean a dominant right cerebral hemisphere. The simplest measure, although not always an accurate one, of hemispheric dominance, is the handedness. Thus, a person having right-cerebral-hemisphere dominance is usually left-handed. The dominance for handedness and for language performance is usually, although not always, in the same hemisphere. Of course, right-brainedness does not always occur in a person whose performance in language is defective, but it does occur in his family. Moreover, when one type of hereditary language defect occurs in a family, other types are likely to appear in members of the same family. Thus, in the family of the stutterer, there are cases of late development of speech, as well as reading disabilities and so on. It seems then, that one is dealing with a hereditary syndrome. A possible explanation of this fact lies in what has been learned of the language function by a study of aphasia: the language function is regulated by the dominant hemisphere, the opposite hemisphere having little, if anything, to do with wording. The patients concerned have a combination of opposing dominance. They are those who have inherited a tendency toward a dominant right as well as a dominant left hemisphere. This inheritance sets the stage for poor language performance in any of the respects already described. These children with a poor hereditary setup for language can improve their performance with careful training. To improve performance, it is well to recognize the fundamental lack of ability, for unless one does, methods planned for improvement will miss their point. Furthermore, unless one understands the interrelation between different parts of the language process,—talking, reading and hearing words,—one misses a chief avenue of therapy in the field of language problems.

319 Longwood Avenue

# SULFATHIAZOLE OINTMENT IN THE TREATMENT OF PYOGENIC DERMATOSES\*

EARL A. GLICKLICH, M.D†

BOSTON

SINCE the advent of sulfanilamide and its derivatives, a beneficial clinical result in many dermatologic diseases has been effected. Beinhauer, Knoll and Perrin<sup>1</sup> observed the response to sulfathiazole, given orally, in 103 patients with sixteen dermatologic diseases. During the course of the oral administration of the drug, many toxic symptoms may arise, such as headache, nausea, fever, burning and itching of the eyes, injection of the scleras and conjunctivas, dermatitis and exquisitely tender and swollen joints, with effusion, leukopenia, hematuria and anuria.<sup>2</sup> Moreover, Spink and Paine<sup>3</sup> treated 16 patients with localized staphylococcal lesions, in 15 of whom the organisms were found in the blood stream. After sterilization of the blood stream by oral sulfathiazole, organisms could still be cultured from the localized lesions. Thus, it seems unwise to subject patients with minor pyogenic dermatoses to the oral administration of the drug, since the toxic manifestations may be severer than the disease and the potential danger of invasion of the blood stream from localized lesions exists even after the blood has been sterilized.

A much simpler method in treating the pyogenic dermatoses is indicated. MacKenna<sup>4</sup> observed that when crushed M and B 693 was dusted on cases of impetigo and ecthyma and covered with zinc paste and a light dressing, the time required to cure the average case was reduced. The same observation with sulfathiazole has been made at the Boston City Hospital since November, 1940. A crude ointment was made by trituration of sulfathiazole tablets and mixing of the powder in a base containing equal parts of lanolin and boric ointment. A more refined ointment was then obtained‡ in which the sulfathiazole was in a suspended state and the size of the particles in suspension approached that of a colloidal one.

Forty-two patients were treated with the crude and refined ointments, with satisfactory results. Twenty had impetigo, 7 pyoderma, 7 eczematoid dermatitis, 1 a recurrent herpes simplex with secondary infection, 1 a herpes zoster with secondary

infection, 3 infantile eczema with secondary infections, 2 disseminated neurodermatitis with secondary infection, and 1 a stasis eczema with secondary infection. Cultures were obtained in 11 of these cases, and the predominant organism was found to be a hemolytic *Staphylococcus aureus* (Table 1).

The patients were instructed to cleanse the involved areas once daily with soap and water, to

TABLE 1. Results of Bacteriologic Studies.

PATIENT	Disease	ORGANISM FOUND IN CULTURE
D. C.	Impetigo	Hemolytic <i>Staph. aureus</i>
W. C.	Impetigo	Hemolytic <i>Staph. aureus</i>
B. D.	Impetigo	Hemolytic <i>Staph. aureus</i>
J. M.	Impetigo	Hemolytic <i>Staph. aureus</i>
J. L.	Pyoderma	<i>Staph. albus</i> , a few colonies of <i>Staph. aureus</i>
S. E.	Pyoderma	<i>Staph. albus</i> , some hemolytic
A. L.	Pyoderma	Hemolytic <i>Staph. aureus</i> ; a few colonies of hemolytic streptococci
T. R.	Eczematoid dermatitis	Hemolytic <i>Staph. aureus</i> and streptococci
S. D.	Eczematoid dermatitis	Hemolytic and nonhemolytic <i>Staph. aureus</i>
T. D.	Infantile eczema with secondary infection	Hemolytic <i>Staph. aureus</i>
P. C.	Stasis eczema with secondary infection	Nonhemolytic <i>Staph. aureus</i>

remove all crusts, and to apply the ointment every two hours during the day and once before retiring. The ointment was applied frequently, since Fleming<sup>5</sup> observed that bacteria and peptones inhibit

TABLE 2. Response of Lesions to Sulfathiazole Ointment.

Disease	No. of Cases	Average Healing Time, days
Impetigo	20	4.6
Pyoderma	7	3.7
Eczematoid dermatitis	7	6.7
Recurrent herpes simplex with secondary infection	1	4.0
Herpes zoster with secondary infection	1	9.0
Infantile eczema with secondary infection	3	6.0
Disseminated neurodermatitis with secondary infection	2	3.0
Stasis eczema with secondary infection	1	4.0
Average		5.2

the bacteriostatic action of sulfanilamide and since peptones are produced by the action of the proteolytic ferments of disintegrating leukocytes on proteins.

The length of time for the pyogenic lesions to respond was from three to nine days, the average being five days (Table 2). The strength of the

\*From the Department of Dermatology and Syphilology, Boston City Hospital.

†Formerly, resident in dermatology and syphilology, Boston City Hospital.  
‡The refined ointment was supplied through the kindness of Abbott Laboratories, North Chicago. It consisted of a 5, 10 and 15 per cent suspension of pure sulfathiazole powder in an ointment preparation containing 4: benzylamine oleate, mineral oil (premier, white), petrolatum alba U.S.P., beeswax (U.S.P.) and distilled water.

ointment, whether it was 5, 10 or 15 per cent, made very little difference in the rate of rapidity with which the lesion tended to heal. When patients with impetigo who were treated with sul-

was instructed to wash the lesions once daily with soap and water and to apply a 10 per cent sulfathiazole ointment (refined form) to the lesions every 2 hours during the day. In 4 days, the superficial infection, as evidenced by crusting and oozing, had disappeared, and healing took place in 8 days (Fig. 2).

TABLE 3. Comparison of Results in Impetigo.

PREPARATION	NO OF CASES	AVERAGE HEALING TIME  days
Sulfathiazole ointment (5, 10 and 15 per cent)	20	4 6
Ammoniated mercury ointment (2 per cent) <sup>a</sup>	25	5 0
Compound chlorhydroxyquinoline ointment <sup>a</sup>	25	4 7
Metaphen (1 500) in flexible collodion <sup>7</sup>	234	8 0
Ammoniated mercury and colloidal Faolin lotion <sup>3</sup>	79	15 0
Ammoniated mercury (2 per cent) and yellow oxide of mercury (0 5 per cent) ointment <sup>a</sup>	32	26 9

fathiazole ointment were compared with those treated with other medications, the results were equivalent or more satisfactory (Table 3).

The following are typical case reports:

CASE REPORTS

CASE 1. W. S., a 17-year-old boy, was admitted to the Boston City Hospital in January, 1941, with impetigo of the face and chin of 1 week's duration. No results were obtained from the use of various local medications. Examination revealed multiple, heavily crusted, oozing lesions on the left side of the face and chin, which were covered

In the 42 patients treated with the crude and refined forms of the sulfathiazole ointment, no local toxic effects were observed. To determine whether absorption of the sulfathiazole took place into the blood stream, 5 gm. of sulfathiazole, in ointment form, was placed on the arms of 4 patients, 2 with normal skin and 2 with generalized erythroderma and secondary infection. The preparation was allowed to remain in place for forty-eight hours by the aid of dressings. During this period, samples of blood were collected at the end

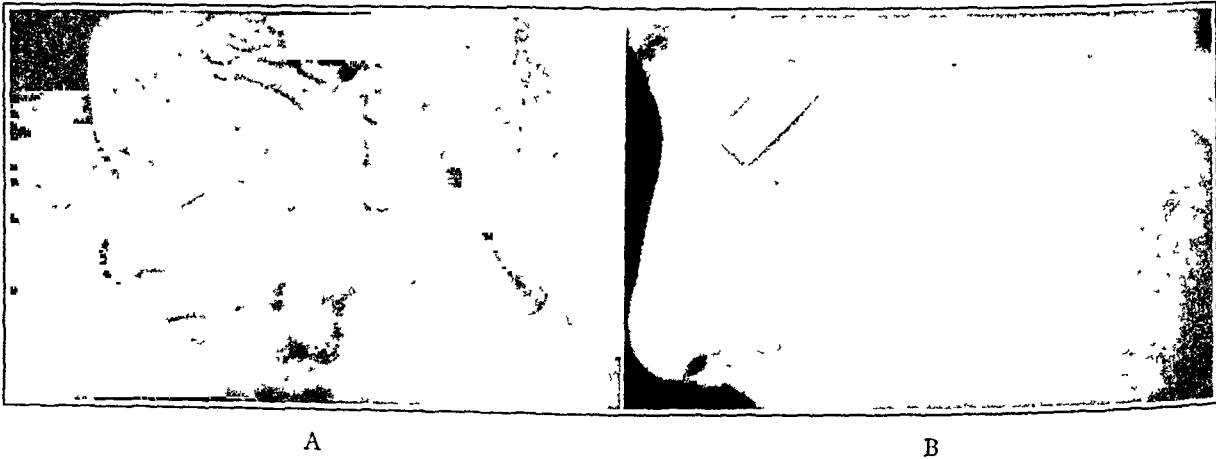


FIGURE 1.  
A shows impetigo of the face on admission to the hospital; B shows the same area after four days' use of 5 per cent sulfathiazole ointment (crude form).

by a yellowish medicament. The patient was instructed to remove the crusts with soap and water and to apply a 5 per cent sulfathiazole ointment (crude form) to the lesions every 2 hours during the day. The patient responded, and was discharged in 4 days with all the lesions healed and with very little evidence on his face of where they had been present (Fig. 1).

CASE 2. T. L., a 22-year-old woman, entered the Out-Patient Department of the Boston City Hospital in March, 1941, with an infectious eczematoid dermatitis involving the pinna and external auditory canal of the left ear of several weeks' duration. Examination showed an oozing, crusting dermatitis, with moderate edema. The patient

of six, nine, twelve, twenty-four and forty-eight hours. At the times when blood was collected, all urine was saved. Sulfathiazole levels were determined on both the blood and urine specimens, and it was found that minute amounts of the drug were absorbed into the blood stream and excreted into the urine. Thus, it was concluded that sulfathiazole in ointment form is less likely to produce the systemic toxic manifestations that one may observe during the administration of the drug orally.

## SUMMARY AND CONCLUSIONS

Forty-two patients with eight different dermatologic diseases, which were caused by pyogenic organisms (mostly hemolytic *Staphylococcus aureus*) per se or were secondarily infected, were treated with an ointment containing sulfathiazole.

The strength of the sulfathiazole made little difference, the infections cleared more quickly, as a rule, than infections treated by other means, no

of the blood stream from localized lesions can occur after discontinuance of the drug orally, and because the use of the drug should be reserved for far more serious illnesses.

## REFERENCES

1. Benham, L. B., Knoll, A. F., and Perrin, S. R. Clinical response of certain dermatologic diseases to sulfathiazole. *Arch. Dermat. & Syph.* 43:621-67, 1941.
2. Glicklich, E. A., and Sherman, D. S. Toxic effects of sulfathiazole used in treatment of chancreoid infection. *Arch. Dermat. & Syph.* 43:992-96, 1941.



A

B

FIGURE 2

A shows an impetiginous eczematoid dermatitis involving the pinna and external auditory canal, B shows the same area after four days' treatment with 10 per cent sulfathiazole ointment (refined form)

toxic effects were observed, and the application of sulfathiazole to the skin for forty-eight hours caused only insignificant amounts of the drug in the blood stream.

From the results obtained by this method, it is believed that the use of the sulfonamides, orally, in the treatment of minor pyogenic dermatoses is not warranted because of the danger that toxic manifestations, which can be more serious than the dermatosis itself, may develop, because invasion

3. Sprink, W. W., and Paine, J. R. The local use of sulfathiazole in the treatment of staphylococcal infection: preliminary report. *Minnesota Med.* 23:615-618, 1940.
4. McKenna, R. M. B. Local treatment with sulphonamide. *Brit. M. J.* 2:99, 1940.
5. Fleming, A. Observations on the bacteriostatic action of sulfanilamide and M & B 693 and on the influence thereon of bacteria and peptone. *J. Path. & Bact.* 50:69-81, 1940.
6. Carpenter, C. C. Treatment of impetigo contagiosa with compound chloroxydrololone ointment. *Arch. Dermat. & Syph.* 37:307, 1938.
7. Hollander, L., and Hecht, J. J. A new auxiliary treatment for impetigo contagiosa. *Am. J. Dis. Child.* 48:269-271, 1934.
8. Pratt, A. G., Imhoff, R. E., and Decker, H. B. Impetigo contagiosa treated with ammoniated mercury-collodion lotion. *J. M. Soc. New Jersey* 36:442-447, 1939.

# HEMATEMESIS DUE TO RUPTURE OF AN AORTIC ANEURYSM

## Report of a Case

BORIS KAPLAN, M.D.\*

NEW BEDFORD, MASSACHUSETTS

THE history of aneurysm is very old. Galen<sup>1</sup> knew external aneurysm well, and in the second century, Antyllus<sup>1</sup> devised his operation of incising and emptying such a sac, inclosed between ligatures. Internal aneurysm was recognized first by Fernelius<sup>1</sup> in the sixteenth century. Later in the same century, Paré<sup>2</sup> suggested the relation of aneurysm to syphilis. Lancise,<sup>3</sup> in 1728, classified aneurysms, but not in the modern sense. Hunter,<sup>3</sup> in 1757, used the terms "true" and "false" in the modern sense and also described the symptoms of pressure he encountered in 5 cases of aneurysm. Corvisart,<sup>4</sup> in 1812, described various signs and symptoms; he called attention to the thrill, retro-manubrial dullness on percussion and inequality of the pulses. Oliver,<sup>5</sup> in 1878, described the tracheal tug. Thoma,<sup>6</sup> in 1888, wrote concerning the pathology of aneurysms. Döhle,<sup>7</sup> in 1895, discussed the microscopic changes in syphilitic aortitis, and finally Reuter,<sup>8</sup> in 1906, described the *Treponema pallidum* in the wall of the aorta in aortitis, and by so doing established the importance of syphilis as a cause of aneurysm.

The disease occurs more frequently in males than in females, in a ratio of 5:1. It is five times more frequent in Negroes than in Whites. Although aneurysm occurs at all ages, the greatest incidence is between thirty-five and fifty-five. Boyd,<sup>9</sup> in an analysis of 4000 cases of aortic aneurysm, states that post-mortem statistics indicate that aneurysms account for 0.1 to 0.5 per cent of deaths in American cities. According to Kampmeier,<sup>10</sup> the incidence of this condition has decreased by more than half in the past decade.

According to Boyd, the ratio of aneurysm in various portions of the aorta is approximately 10:7:3:1 for the ascending, transverse and descending segments of the aortic arch and the descending thoracic aorta, respectively.

In practically all cases, syphilis is the cause. Arteriosclerosis, tuberculosis, trauma and mycotic infections play a very minor role.

The diagnosis is based on signs and symptoms and x-ray findings. The physical signs of thoracic aneurysm are too well known to require enumeration here. It may be comparatively easy to recognize a classic case of aneurysm after a careful physical examination. However, in many cases,

as in an aneurysm of the upper descending aorta, the process may be so latent and the signs so negligible that recognition may tax the ability of the most experienced clinician. In such cases, the diagnosis is made on suspicion or incidentally on x-ray examination. Osler<sup>11</sup> wrote, "There is no disease more conducive to clinical humility than aneurysm of the aorta."

The following case of aneurysm of the descending segment of the aortic arch is reported because the condition was undiagnosed and because the patient died of an unusual complication—rupture into the esophagus.

### CASE REPORT

A 58-year-old clerk entered St. Luke's Hospital because of hematemesis. For the previous 2 or 3 weeks, the patient had complained of "gas pains" in the epigastrium coming on directly after meals and relieved by saleratus and pills given by his physician. There was no nausea, vomiting, diarrhea, constipation or specific intolerance to fatty or fried food. The patient had been working during these 2 weeks. On the morning of admission, he suddenly felt a general weakness and vomited about a pint of bright-red blood. He was immediately taken to the hospital, where he again brought up a glassful of bright-red blood.

The patient had had pneumonia 1 year previously and an acute upper respiratory infection 2 weeks previously that had since disappeared. He had had no dyspnea, orthopnea, cyanosis or edema. His mother had died of cancer. His wife and a son were well. A daughter died, at the age of 16, of heart trouble.

Physical examination showed a well-developed, fairly well-nourished man who was somewhat pale and extremely apprehensive. The temperature was 96°F., the pulse 78, and the respirations 20. The pupils were round, regular and equal, and reacted to light and accommodation. The scleras were clear. The conjunctivas were moderately pale. The mucous membrane of the mouth was of fair color. The tongue protruded in the midline, without deviation.

There was no stiffness or retraction of the neck. No lymph nodes were palpable. No dullness or rales were present in the lungs. The breath sounds were normal. The heart was not enlarged to percussion, and the sounds were of good quality. The rhythm was regular, with no murmurs. The blood pressure was 80/60. The abdomen showed no spasm or tenderness, and no masses were felt. The extremities were symmetrical, without ulcerations. The knee jerks were normal.

Examination of the blood showed a red-cell count of 2,600,000 with 54 per cent hemoglobin, and a white-cell count of 12,400 with 61 per cent neutrophilic leukocytes, 25 per cent lymphocytes, 4 per cent large mononuclears and 10 per cent polynuclear band cells. The red blood cells were hypochromic. The blood Kahn reaction was negative. The urine was normal.

\*Assistant in medicine and in charge of the Gastro-Intestinal Clinic, St. Luke's Hospital, New Bedford.

The diagnosis was bleeding peptic ulcer.

The patient's blood was typed. He was placed on a diffied Meulengracht's<sup>12</sup> diet and aluminum hydroxide. stopped vomiting, and his condition in the next several days improved rapidly. On the 7th hospital day, he developed auricular fibrillation, and dullness and diminished breath sounds in the left chest. A film taken with a portable x-ray apparatus revealed a massive collapse of the left lung. The right lung was clear. On the following day, shortly after midnight, the patient began to vomit huge amounts of bright-red blood, and died before any possible treatment could be given.

*Autopsy* (8 hours post mortem). Gross examination revealed blood in the mouth. In the descending portion

or 6 mm. in diameter and admitted the tip of a forceps. A little blood was present in the esophagus. The extension of the aneurysm through the bronchial wall was similar but smaller.

The stomach was greatly distended by blood, much of which was clotted, and the rugae were flattened. The mucosa showed a mild congestion, but no ulcerations were seen in it or in the duodenum.

Microscopic study of the aorta and the wall of the aneurysm revealed many foci of new blood vessels and monocytes in the media and a variable widening of the adventitia in which an increase of fibrous tissue and an invasion of lymphocytes and plasma cells, especially around the blood vessels, were noted. Part of the mass lining the aneurysm consisted of acellular fibrin, frequently in laminated form, and part had a definite thrombus structure. Over the extensions into the bronchus and esophagus, the wall was very thin and consisted of only a few strands. The lung alveoli and the small bronchi contained no blood.

Anatomical diagnoses: syphilitic aortitis, with aneurysm of descending portion of arch, erosion of thoracic vertebrae, erosions into the left bronchus and esophagus, and hemorrhage into the esophagus.

### DISCUSSION

So-called "gas pain" in the abdomen experienced by the patient on a few occasions before admission to the hospital is suggestive of many conditions. It may be a sign of organic as well as functional disease. But when the patient also suffers an episode of severe hematemesis, grave organic disease is almost surely present. Bleeding peptic ulcer is the commonest cause of such symptoms. It is true that a number of other conditions may cause hematemesis—carcinoma or, more rarely, lymphoma or sarcoma of the stomach, aortic aneurysm, mesenteric venous thrombosis, carcinoma of the gall bladder eroding the duodenum, acute esophagitis, esophageal varices due to cirrhosis of the liver, abdominal trauma, thrombocytopenic purpura, carcinoma of the pancreas eroding the duodenum, acute gastritis and Banti's disease. However, such causes of hematemesis are comparatively rare.

Because the physical examination and laboratory findings were essentially negative, except for acute secondary anemia, in the case presented above, peptic ulcer was considered the most probable diagnosis. The patient responded very well to rest and diet, and his general condition was good. On the seventh day, he suddenly developed auricular fibrillation and atelectasis of the left lung. Because of these new findings, attention was focused on the chest, and for the first time there was some doubt. Was the bleeding from the upper gastrointestinal tract, lungs or great vessels? Unfortunately, the patient suddenly died the following day from the massive hematemesis, and there was no opportunity for further study.



FIGURE 1. Post-Mortem Specimen.

The arrow marks the area of perforation of the aneurysm into the esophagus.

The aortic arch was a saccular aneurysm, which extended from the 4th to the 9th thoracic vertebra and had eroded the left side of the 5th to 8th dorsal vertebral bodies. It was adherent to the lower portion of the esophagus at a point 5 to 7 cm. above the cardiac orifice of the stomach and also to the left main bronchus about 1 cm. above the bifurcation, and had extended through the walls of both these structures, forming oval protrusions into their lumens. The defect in the esophageal wall measured by 2.3 cm., and the dome-like elevation of the sac wall was gray except at its lower edge, where there was an opening from the sac into the esophagus, which was 5



## SUMMARY AND CONCLUSIONS

A case of a syphilitic aneurysm of the descending portion of the arch of the aorta, with rupture into the esophagus, is reported.

Although aneurysm has long been recognized as a clinical entity, the silent forms are rather unusual and may present a difficult diagnostic problem, especially if one does not consider such a possibility. Surprise and humility of the attending physician can be prevented if each patient with a severe hematemesis of unknown origin is immediately fluoroscoped in a horizontal position; care should be taken to avoid all abdominal palpation. Thus, no possible harm can be done to the patient, and aneurysms of the aorta can be ruled out.

98 Cottage Street

## REFERENCES

1. Osler, W. *The Principles and Practice of Medicine*. Eighth edition. 1226 pp. New York: D. Appleton and Co., 1912. P. 847.
2. Major, R. H. *Classic Descriptions of Disease*. 630 pp. Springfield, Illinois: Charles C Thomas, 1932.
3. Erichsen, J. E. *Observations on Aneurism*. 524 pp. London: Sydenham Society, 1844.
4. Corvisart, J. N. *An Essay on the Organic Diseases and Lesions of the Heart and Great Vessels*. 344 pp. Philadelphia: Anthony Finley, 1812.
5. Oliver, W. S. Physical diagnosis of thoracic aneurism. *Lancet* 2:406, 1878.
6. Thoma, R. Untersuchungen über Aneurysmen. *Virchows Arch. f. path. Anat.* 111:76-113, 1888.
7. Döhle, E. Über Aortenerkrankung bei Syphilitischen und deren Beziehung zur Aneurysmenbildung. *Deutsches Arch. f. klin. Med.* 55:199-210, 1895.
8. Reuter, K. Neue Befunde von *Spirochaete pallida* (Schaudinn) im menschlichen Körper und ihre Bedeutung für die Ätiologie der Syphilis. *Ztschr. f. Hyg. u. Infektionskr.* 54:49-64, 1906.
9. Boyd, L. J. A study of four thousand reported cases of aneurysm of the thoracic aorta. *Am. J. M. Sc.* 168:654-668, 1924.
10. Kampmeier, R. H. Saccular aneurysm of the thoracic aorta: a clinical study of six hundred and thirty-three cases. *Ann. Int. Med.* 12:624-651, 1938.
11. Osler: cited by Kampmeier.<sup>10</sup>
12. Meulengracht, E. Behandlung von Hämatemesis und Melæna ohne Einschränkung der Nahrung. *Klin. Wchnschr.* 13:49, 1934.

## MEDICAL PROGRESS

## LICHEN PLANUS: DIAGNOSIS, ETIOLOGY AND TREATMENT

PERRY C. BAIRD, JR., M.D.\*

BOSTON

ALTHOUGH lichen planus has for generations engaged the profoundest interest of physicians the world over, it remains a baffling problem and still constitutes a decided challenge to medical science. The disease is all the more absorbing in its interest because it represents such a clear-cut morphologic entity. It is an appealing and stimulating subject for investigation concerning both interpretation and treatment.

Of the neurogenic, toxic and microbic theories of causation, the first is probably the most popular among writers at present. However, very little convincing evidence regarding causation has accumulated, and no tangible clues to the specific etiology have been found. The treatment has not advanced beyond the empirical stage, and is still chiefly a matter of mercury, arsenic, bismuth and x-ray. However, the use of vitamin B complex, as recommended in a recent publication by Burgess,<sup>1</sup> may prove to be a worthy contribution. The results obtained by Burgess were so favorable as to suggest that his observations will lead to the discovery of some therapeutic method as effective as but less dangerous than some of the procedures now in use. Possibly, this improved form of treat-

ment will be some fraction of the vitamin B complex.

The diagnosis of lichen planus is not difficult in most cases, and yet the behavior of the disease is so varied as to present occasional hazards. Certainly, it is not easy to learn to diagnose lichen planus by textbook descriptions or photographs any more than it is with many other skin diseases. Nevertheless, after one has studied with care a few typical cases, appropriate diagnostic acumen for this disease may be acquired.

The primary lesion of lichen planus is a shiny, flat-topped angular papule, which nearly always presents a violaceous tinge. This lesion is so characteristic that, if examined carefully, it is not likely to be confused with other primary lesions. The papules of lichen planus may develop in rows along lines of scratch. Favorite areas of distribution include the flexor surfaces of the wrists, the inner aspects of the legs and thighs, the penis and the mucous membranes of the mouth and lips. In contrast with the usual tendency toward angular morphology, lichen planus may take the form of ring-shaped lesions, which are encountered especially in the region of the wrists and genitalia. The mucous-membrane changes may be of the nature of silvery stippling, or a flat whitish lacelike network, or whitish patches and streaks. The mucous-membrane lesions may resemble leuko-

Reprints of articles in this series are not available for distribution, but the articles will be published in book form. The current volume is *Medical Progress: Annual, 1940* (Springfield, Illinois: Charles C Thomas Company, 1941. \$4.00).

\*Associate in dermatology, Peter Bent Brigham Hospital; lecturer on industrial hygiene, Harvard University.

plakia, with which lichen planus is often confused. In extent, the disease may vary from a few papules to involvement of practically the entire body surface. The expert must learn to recognize atrophic, hypertrophic, bullous and other forms of lichen planus. Pruritus may vary in degree from mild discomfort to intolerable agony, sometimes leading to suicide.

Lichen planus must be differentiated from other papulosquamous eruptions, such as psoriasis, parapsoriasis and secondary syphilis. No great difficulty should be encountered in distinguishing lichen planus from pityriasis rosea, tinea versicolor and seborrheic dermatitis. A typical case of lichen planus bears no real resemblance to psoriasis. On the other hand, it is worth remembering that many of the lesions in some of the borderline cases of lichen planus may be decidedly psoriasiform. Such lesions show layered, silvery scaling difficult to distinguish from psoriasis and a distinctive erythematous tint strongly suggestive of psoriasis. In psoriasis, the scales are usually thicker and more abundant, and bleeding points may be found. Psoriatic plaques are formed by peripheral extension of the initial papular lesions, whereas lichen planus patches are formed by coalescence of papules. In psoriasis, the elbows and knees seldom escape involvement; in lichen planus, the flexor surfaces of the wrists and the inner aspects of the legs and thighs are areas of predilection. Lichen planus is frequently seen on the mucous membranes of mouth and lips, whereas psoriasis is almost never found in these areas. Both conditions may involve the penis.

In patients who present a papulosquamous skin eruption resembling both psoriasis and lichen planus, the differentiation may remain quite difficult until the skin has been examined completely. Then it is usually possible to demonstrate diagnostic points that swing one's judgment decidedly one way or the other. The finding of characteristic lichen planus papules or typical mucous-membrane lesions quickly settles the matter.

It is advisable to perform blood Wassermann, Hinton and Kahn tests in every case of lichen planus, and only in this way can one be sure to avoid occasional errors in confusing this disease with papulosquamous secondary syphilis.

Lichen planus limited to the oral mucous membranes is not difficult to recognize because of its peculiar morphology, which consists in a whitish stippling, patches and streaks or a whitish lace-like network. Lichen planus of the oral mucous membranes is less likely to be confused with leukoplakia if there are lesions elsewhere in the skin.

Lichen planus may be limited in its distribution to the vulva and in this way becomes of considerable interest to surgeons, gynecologists and obstetricians, who must differentiate it from kraurosis vulvae and leukoplakia. Biopsy must be carried out at times, to aid in the differential diagnosis, particularly if there are no lesions elsewhere over the body to help in arriving at a decision. Because of this circumstance, the histologic picture of lichen planus is probably at times of even greater usefulness to gynecologists than it is to dermatologists.

Authorities agree that the papules of lichen planus possess a histologic structure that may be regarded as pathognomonic and permits accurate diagnosis from biopsy material. A characteristic feature is the limitation of the cellular infiltration to a regular band in the upper cutis.<sup>2</sup> The lower border of this lymphocytic infiltration is sharply outlined, and the upper border lies just subjacent to the basal-cell layer. Among other features of the histopathology, McCarthy<sup>3</sup> includes the following: well-defined, circumscribed (papular) lesions; hyperkeratosis, without parakeratosis; widening of the stratum granulosum; acanthosis, with formation of ill-developed rete cones; hazy outline between epithelium and corium; space formation at the cutaneous epithelial border; dilated blood vessels of the papillary and subpapillary layers; and occasional giant cells (Sabouraud).

Cases of both familial and conjugal lichen planus have been reported. It is of great interest to study these case histories, because of the light that they seem to cast on the etiology of this strange disease. The interpretation of lichen planus as a familial disease was apparently first suggested by Hallopeau and Leredde<sup>4</sup> in 1900, although several observers, including Lustgarten,<sup>5</sup> Brocq<sup>6</sup> and Ormerod,<sup>7</sup> had reported cases with a familial background.

Of approximately 60 cases of familial lichen planus reported in the literature, some of the most unusual have been summarized by Saffron<sup>8</sup> as follows: an acute attack that developed in a mother while she was treating a daughter who had the disease (Brocq<sup>6</sup>); hypertrophic lichen planus in three generations—mother, son and grandson (Joseph<sup>9</sup>); an acute form that developed in two sisters living apart, six weeks after the death of their father (Little<sup>10</sup>); the annular, atrophic variety in two sisters, with the lesions confined to the legs (Samuel<sup>11</sup>); acute lichen planus, in two brothers who were not living together, complicated by glandular and splenic enlargement (Bettmann<sup>12</sup>); typical lesions in a ten-month-old nursing whose mother had lichen planus (Wende<sup>13</sup>); lichen planus verrucosus in a father and son (Von Ken-

nel<sup>14</sup>); lichen planus in the father, son and daughter of a family of four (Veiel<sup>15</sup>); and three brothers who had lichen planus (Scheer<sup>16</sup>).

The occurrence of 4 cases of lichen planus in one family has been reported by Saffron,<sup>8</sup> who concludes that the familial occurrence is an argument for the neurogenic theory of the disease.

The family consisted of father, mother, four sons and a daughter. None of the children had lived with the parents or with one another for ten years. All members of the family were well educated, sensitive and of above average intelligence. The mother, at the age of fifty-two, developed acute lichen planus in 1921 at a time when, presumably, the children were living with the parents. Eleven years later, in 1932, one son, aged thirty-six, developed the disease. In 1936, fifteen years after the mother's first attack, another son, aged thirty-seven, developed lichen planus, and in this same year the mother had her second attack. In 1938, seventeen years after the mother's first attack, still another son, aged thirty-eight, had an acute widespread attack of lichen planus; in the following year, this son had a second attack. The mother's first attack lasted five months, and the second eight months. The first son's attack lasted three months, and the second son's six months. The third son's first attack lasted three months, and his second eight months. All attacks in this family were associated with severe pruritus except for the mild attack in the first son, who had only slight itching. The first son was a salesman, the second a dentist, and the third a factory manager.

Lichen planus of the oral cavity in twins has been reported recently by Epstein<sup>17</sup> as an occurrence previously unknown in the literature. Epstein interprets these cases as evidence favoring both the theory of familial predisposition and the theory of infection. However, his patients displayed indisputable nervous factors and, therefore, could be used in support of the neurogenic hypothesis. It is not illogical to presume that in some of the cases of lichen planus there may be an etiologic interplay of all three of these elements. Abstracts of the 2 cases are as follows:

A 25-year-old man was seen in January, 1939. He had noticed white lesions in his mouth for about 2 months. On examination, he presented numerous confluent reticular lesions covering nearly all the mucous membranes of the cheeks. The appearance was typical of lichen planus, and the additional finding of two annular lesions on the tongue helped to substantiate the diagnosis. In the course of 6 months, the patient consumed 60 cc. of potassium arsenite solution (*U.S.P.*), and the eruption cleared except for a few lesions. Treatment was then changed to vitamin B complex, and good condition was maintained so long as he continued vitamin B complex capsules. Each time he stopped taking these capsules, the disturbance showed a tendency to recur.

The identical twin of this patient was seen in February, 1941, 2 years following his brother. This patient began to notice lesions on the mucous membranes, the middle of the tongue and the lower lip about 8 months after his twin brother had begun to notice symptoms. The similarity of the eruption in the 2 cases was so striking that the patient himself made the correct diagnosis. Examination revealed a picture similar to that described in the case of his brother, with the added finding of a typical annular lesion on the lower lip. The patient treated himself by means of vitamin B complex in dosage up to 9 capsules a day. His condition improved greatly.

Interesting features of these 2 cases of lichen planus are the following: the patients were identical twins; no other members of the family were affected—neither their parents, with whom they lived, nor their brother, with whom they worked, had the condition; both patients were nervous and high strung and admitted hurrying and worrying all the time, and both observed that they were much better when not worried or excited; the clinical picture in the 2 cases was almost identical.

Similarity of symptoms in familial lichen planus has been reported too often to be considered a coincidence. Little's<sup>18</sup> observation of lesions confined to the mucous membranes of the mouth in mother and son corresponds to the cases reported by Epstein.

Spitzer,<sup>19</sup> in 1924, collected from the literature 46 cases of familial lichen planus, in 7 of which husband and wife were affected. Since 1924, 12 additional reports of familial lichen planus have appeared. Of these, only 3 have been conjugal in nature.<sup>20-22</sup>

Of the 10 known cases of conjugal lichen planus, the most recent was reported in 1937 by Goodman and Sulzberger,<sup>20</sup> who encountered this interesting example in their office practice.

The wife, aged 45, when first seen in August, 1935, gave a history of having had a pruritic skin disorder for 8 months. She stated that her husband had complained of itchy lesions on his legs for more than a year prior to the onset of her trouble. Examination disclosed a typical lichen planus consisting in widely distributed, purplish, flat-topped papules. Some of these had an annular grouping. The buccal mucosa showed a network of minute whitish lesions, and there were whitish patches involving the perianal and perivulvar areas. The findings were so typical of lichen planus as to leave no possible doubt regarding the diagnosis. The lichen planus cleared in large part in 3½ months following x-radiation, bismuth and mercury.

The patient's husband was a 53-year-old salesman who was seen, shortly after his wife's satisfactory recovery, in January, 1936. His lichen planus had been slowly extending during his wife's period of recovery under treatment. On examination, he showed typical hypertrophic lichen planus on the legs and ordinary lichen planus elsewhere. There were scattered angular flat-topped papules and occasional ringed forms. One large, annular lesion was present on the penis. Involvement of the lower lip

and buccal mucous membrane left no further doubt regarding diagnosis. This patient recovered satisfactorily following x-ray therapy and mercury. The hypertrophic patches were resistant at the start, but later they were reduced considerably by applications of trichloroacetic acid.

The occurrence of conjugal lichen planus seems to be an argument for the theory of infection.

No discussion of the etiology of lichen planus could be considered adequate without further mention of the theory of infection and the evidence for it. In 25 out of 28 typical cases, Jacob and Helmbold<sup>23</sup> isolated a gram-negative anaerobic bacillus, morphologically resembling those of the colon-typhoid group, which grew freely on a semisolid glucose human-serum medium containing pieces of human tissue. In sections of the lesions, they were able to demonstrate the organism but could not do so in normal skin or in other types of papular skin disorders. By inoculation of the skin of normal persons with this organism, they occasionally succeeded in producing lesions that resembled lichen planus both clinically and histologically.

According to Guttman,<sup>24</sup> modern work has failed to show any connection between the nervous system and lichen planus. Other observers, however, including Ormsby,<sup>25</sup> Pusey,<sup>26</sup> MacLeod<sup>27</sup> and O'Donovan,<sup>28</sup> believe that the disease can be precipitated by mental disturbance. Ramel<sup>29</sup> has reported the case of a woman who developed lichen planus a few days after severe mental trauma; she resisted the usual forms of treatment but recovered following psychotherapy, which brought to consciousness a typical Freudian complex. Eller<sup>30</sup> observed that, during a serious fall in the stock market, acute lichen planus developed among a number of business men who had suffered financial losses. The wife of one of these was affected similarly.

To determine whether certain dermatoses occurred more frequently among nervous patients than among the general population, Goldsmith<sup>31</sup> compared their relative incidence in proportion to the total number of new patients attending the West End Nerve Hospital with their relative incidence in proportion to the total number of new patients attending a general hospital, the University College Hospital. Lichen planus was found by Goldsmith to be only half as common at the nerve hospital.

Culver<sup>32</sup> believes that there is no nervous element in the etiology of lichen planus and quotes in support of this the lack of cases in California during World War I. Since the disease is not reportable, no figures are available to prove whether war actually increases, decreases or fails to affect the incidence. Usually, it is assumed that there has been no increase in lichen planus during

wartime and that this constitutes an argument against the theory of nervous origin. On the other hand, it might be reasoned that war creates a type of stress and strain that crowds out minor financial or family worries and perhaps paves the way for a type of adjustment that does not tend to precipitate attacks of lichen planus.

The generally recognized modern therapeutic approach to lichen planus consists essentially in mercury, arsenic, bismuth and x-ray therapy, as previously mentioned. Other methods of treatment include psychotherapy, injections of extracts of the papules, foreign-protein therapy with colon typhoid vaccines or milk, and lumbar puncture. Local applications are useful only as antipruritic agents. Stelwagon<sup>13</sup> has advised that "the patient is to have the benefit of good, plain food, hygienic living, and, when possible, outdoor life and freedom from mental worry or care."

When the disease is extensive, all forms of injection therapy have an advantage over x-radiation. The bismuth therapy of lichen planus has the advantage that it is less apt to be complicated by untoward reactions than arsenic and mercury are. Bismuth may be administered as the salicylate in oil by intramuscular injection in doses of 1 or 2 cc. at weekly intervals, as in the treatment of syphilis. Bismuth is less effective than arsenic but is advisable for use at the start of treatment because its complications are fewer. Arsenic may be substituted if the therapeutic response to bismuth is inadequate.

The French preparation, Énésol, has been very popular in this country for the treatment of lichen planus and has been considered one of the most reliable forms of therapy. This drug, which is a combination of mercury and arsenic, is administered intramuscularly in doses of 1 or 2 cc. once or twice weekly. Eight to sixteen or more injections may be necessary. The usual reactions to mercury and arsenic must be looked for.

Conrad et al.<sup>34</sup> have reported 25 cases treated by the intramuscular injection of bismuth arsphenamine sulfonate (Bismarsen). They employed twelve to twenty-five injections of 0.1 to 0.13 gm. each. Patients showing signs of a mild toxic reaction to Bismarsen—skin changes, drowsiness, stomatitis and puffiness of the legs—were given large dosage of vitamin C while the drug was continued, and all these reactions disappeared. In some cases, the drug had to be stopped owing to severer reactions. Conrad and his associates treated hypertrophic, localized and generalized types of lichen planus and concluded conservatively that Bismarsen seems to be of value.

Sulzberger<sup>35</sup> recommends that arsenic be administered in the form of a 2 per cent sodium ar-

senate solution containing 1 or 2 per cent phenol. This solution, prepared with sterile water and placed in a sterile container, should be kept in the refrigerator. Injections are given daily by the subcutaneous route. The initial dose is 2 minims, which is increased by 1 minim daily until a dose of 20 to 30 minims (1.5 to 2.0 cc.) is reached. If the eruption disappears or if signs of intolerance develop, the arsenic should be stopped. If necessary, the dosage may be increased to 60 minims (4.0 cc.) daily, and then given in decreasing daily doses until improvement takes place.

Fowler's solution may be given by mouth if the daily subcutaneous injection is not expedient. Sulzberger<sup>35</sup> recommends a mixture containing 1 part of Fowler's solution and 2 parts of compound elixir of pepsin (*N. F.*) or menthol water. Administered in this form, Fowler's solution is more palatable and less irritating to the gastric mucosa. The dose is 10 to 30 drops (0.6 to 2.0 cc.) of the diluted solution three times daily, following each meal.

Arsenic may be administered by mouth in the form of the Asiatic pill (arsenic trioxide). This pill is available in three strengths: 0.002 gm., 0.004 gm. or 0.007 gm. arsenic. At the start, the weakest pill is given three times daily. Later, the dose is increased to the limits of tolerance.

Treatment for four to six weeks is usually necessary before the effects of arsenicals are visible. The treatment, if successful, will bring about relief of itching and disappearance of the lesions, leaving only residual pigmentation and occasionally depigmentation.

In a series of cases of lichen planus some of which had defied the usual treatment for years, Biberstein<sup>36</sup> succeeded in curing 70 per cent by injecting extracts of the papules.

Recent studies by Burgess<sup>1</sup> on the use of vitamin B complex in the treatment of lichen planus are of great interest from the standpoint of both etiology and therapy. His encouraging results are also well worthy of attention because they came about as a consequence of the use of a type of treatment bearing no serious hazards. Burgess points out that the majority of dermatologists have resorted to the theory of neurogenous causation in preference to the parasitic, microbic and toxic. Both he and Goldsmith<sup>31</sup> cite Ramel,<sup>29</sup> who found that violent emotional shock produced the eruption in some cases and that cure resulted from psychoanalytic treatment. Burgess believes that the good results obtained from lumbar puncture and irradiation of certain segments of the spinal column may be ascribed to the psychic value of these procedures. In keeping with these lines of reasoning, Burgess then set out to study the therapeutic effects of vitamin B complex on the theory

of its possible action in relieving the nervous tension of these patients.

Some of the cases studied by Burgess may be briefly abstracted as follows:

CASE 1. Treatment was carried out by means of thiamine chloride given by mouth in daily dosage of 3000 international units and liver extract administered intramuscularly twice weekly in doses of 2 cc. There was lessened irritability in a few days and beginning involution of the lesions in 3 weeks.

CASE 2. Liver extract, given by intramuscular injection in doses of 2 cc. every 2 days, brought about marked regression of lesions in 1 week.

CASE 3. Beminal was given by mouth in daily dosage of 120 cc. and nicotinic acid in daily dosage of 150 mg. Striking regression took place in 4 days.

CASE 4. Marked involution took place in 3 weeks following the use of Beminal by mouth and liver extract by injection.

CASE 6. The response was precisely the same as that in Case 4.

CASE 7. After 6 years' duration, recovery took place in 6 weeks following the use of Beminal and liver extract by mouth.

CASE 8. After 3 years' involvement of the legs and mucous membranes, marked improvement took place in 1 month following the use of Beminal and liver extract by mouth. Complete recovery took place in 2 months.

CASE 9. After 2 years' involvement of the mucous membranes only, complete disappearance of lesions took place in 1 month following the use of brewers' yeast and nicotinic acid by mouth.

CASE 10. A case of 4 months' duration, with involvement of the buccal mucous membrane and tongue, did not respond to yeast, Beminal, riboflavin, nicotinic acid, thiamine chloride, x-radiation, arsenic and mercury.

CASE 12. Lichen planus developed in the course of anti-syphilitic therapy. Brewers' yeast was given by mouth and thiamine chloride by injection. In 1 month, all lichen planus papules were gone.

CASE 14. A case of lichen planus of the dorsal surfaces of the hands of 2 months' duration, with onset following a heart attack, did not respond to vitamin B complex and x-radiation.

CASE 15. Hypertrophic lichen planus located on the inner aspect of the right knee showed improvement with x-radiation but, after 2 months of therapy by means of Beminal by mouth and liver extract by injection, the thickening disappeared completely and was replaced by an area of atrophy.

Burgess states that, in his series of 25 cases, vitamin B complex as a whole, rather than any special constituent, seemed to be effective. He found that such therapy was much less successful if mental unrest continued, and was more effective if nervous stress and strain could be relieved by rest and reassurance.

The itching of lichen planus may constitute a serious symptom; however, it may be entirely absent. The control of pruritus is in some cases beyond the powers of medical science. All forms of therapy known to be of value in bringing about

involution of the lesions are also of assistance in combating the subjective symptoms of this disease. Chloral hydrate is the safest soporific to employ. Sedatives such as phenobarbital may be used, but morphine should be avoided if possible, because of the tendency toward habit formation and its powers of aggravating the itching.

Topical applications in lichen planus are of no value except to help control discomfort. Antipruritic remedies may be made up in aqueous or alcoholic solution or in a vanishing-cream base, and they may contain 0.25 to 1 per cent menthol, 0.25 to 2 per cent phenol, 0.25 to 5 per cent camphor, 0.25 to 1 per cent thymol and 1 to 5 per cent chloral hydrate.

\* \* \*

By full use of all that is known concerning the therapy of lichen planus, gratifying results may be expected in many cases. Some of the patients, however, resist all the usual procedures and suffer from the disease in unabated form for years. There is great need for a more detailed and critical study of these cases from the standpoint of psychiatry, clinical pathology and general medical investigation. There has been scant effort to refute or substantiate the work concerning microbic origin. If the cases were more carefully studied from the historical viewpoint, it is likely that more reports would come forth regarding familial and conjugal incidence, and the interpretation of such cases might become more clear cut.

Lichen planus has many ramifications through the general field of medicine and, as mentioned above, may be limited in its distribution to the mucous membranes of the vulva; it thus becomes of special interest to surgeons, gynecologists and obstetricians. It may appear as a reaction to drugs such as arsenic and the heavy metals, the same chemicals so popular in its therapy. Obviously, it is not purely an external skin disturbance, but a constitutional illness of extraordinary character. Perhaps, the pathologic physiology of lichen planus will not be understood until more is known about what the activities of the sympathetic and parasympathetic nervous systems can do to tissues.

Burgess's<sup>1</sup> work on vitamin B therapy, which gives an entirely new angle to this many-sided subject, may provide a more satisfactory form of treatment, for which there has been a great need as voiced by many dermatologists at the recent meeting of the Academy of Dermatology and Syphilology in New York City. The work of Burgess should be repeated carefully because it really seems "too good to be true." If it is true,

one must find out why vitamin B complex is effective, and it might be of value to investigate whether there is some vitamin B complex fraction of particular value.

A fuller understanding of lichen planus from the neurogenous angle might add a chapter to the rapidly increasing understanding of what the stresses and strains of life can do to the human body, and how these stresses and strains can be offset by vitamins, rest, psychotherapy and other measures.

270 Commonwealth Avenue

## REFERENCES

- Burgess J F The treatment of lichen planus with vitamin B complex *Canad M A J* 44 120 123 1941
- Andrews G C *Diseases of the Skin* 1091 pp Philadelphia W B Saunders Co 1937
- McCarthy J *Histopathology of Skin Diseases* 513 pp St Louis C V Mosby Co 1931
- Hallopeau F H and Leredde L E *Traité pratique de dermatologie* 992 pp Paris J B Baillière & Fils 1900
- Lisagueten S Three cases of lichen planus in the same family *J Cutan Dis* 12 501 1894
- Brocq J *Quelques considérations sur le lichen ruber planus* *Rev gen de der et de therap* 11 209 211 1897
- Ormerod J A Lichen ruber planus *Brit J Dermat* 12 413, 1900
- Saffron M H Familial lichen planus: a report of four cases of lichen planus in one family with a brief review of the literature *Arch Dermat & Syph* 42 653 655 1940
- Joseph M *Lehrbuch der Hautkrankheiten* Eighth edition 477 pp Leipzig Georg Thieme 1915
- Little E G G Lichen planus *J Cutan Dis* 37 639 670, 1919
- Samuel H C Lichen planus annularis in two sisters *Brit J Dermat* 27 321 1915
- Bettmann S Beiträge zur Kenntnis des Lichen ruber Planus *Arch f Dermat u Syph* 75 3 9416 1905
- Wende G W In discussion of Dride Lichen planus acute *J Can an Dis* 32 805 1914
- Verneken J Lichen ruber verrucosus *Zentralbl f Haut- u Geschlechtskr* 30 691 1929
- Veel F Lichen ruber planus als Familienkrankung *Arch f Dermat u Syph* 93 383 387 1908
- Scheer M In discussion of Feit H Lichen planus in mother and child *Arch Dermat & Syph* 20 254 1929
- Epstein S Lichen planus confined to the oral cavity in twins *Arch Dermat & Syph* 45 382 1942
- Little Cited by Juliusberg P Lichen ruber and Pityriasis rubra pilaris In Jadassohn J *Handbuch der Haut und Geschlechtskrankheiten* Vol 7 803 pp Berlin Julius Springer, 1931 P 116
- Spitzer R Über familiären Lichen ruber planus *Arch f Dermat u Syph* 146 474 480 1924
- Goodman J and Sulzberger M B Conjugal lichen planus *Arch Dermat & Syph* 35 1139 1937
- Grange P Lichen plan conjugal *Rev franç de dermat et de vénéréol* 8 221 224 1932
- Weiss A, Spillman L and Rosenthal Lichen plan conjugal et syphilis *Bull Soc franç de dermat et syph* 41 803 1934
- Jacob F M, and Helmhold T R Bacteriologic studies on lichen planus *Arch Dermat & Syph* 27 472 480 1933
- Guttmann E Nerven und Haut In Jadassohn J *Handbuch der Haut und Geschlechtskrankheiten* Vol 4 1490 pp Berlin Julius Springer 1933 P 1222
- Ormsby Cited by Goldsmith<sup>31</sup>
- Pusey Cited by Goldsmith<sup>31</sup>
- MacLeod Cited by Goldsmith<sup>31</sup>
- O Donovan W J *Dermatological Neuroses* London Hegan Paul 1927
- Rame J Cited by Goldsmith<sup>31</sup>
- Eller, J J Neurogenic and psychogenic disorders of the skin *M J* 82 129 670 1929
- Goldsmith W N *Recent Advances in Dermatology* 572 pp Philadelphia P Blakiston's Son & Co Inc 1936 P 113
- Culver G D A clinical study of lichen planus *Arch Dermat & Syph* 1 43 49 1970
- Stelwagon Cited by Sutton R L and Sutton R L Jr *Diseases of the Skin* 1433 pp St Louis C V Mosby Co, 1935 P 220
- Conrad A H, Conrad A H Jr, Mapolet, P, and Weiss R S Lichen planus treated with bismuth orphenamine sulfonate (bis murex)<sup>32</sup> *South M J* 33 721 729, 1940
- Sulzberger M B and Wells J *Dermatologic Therapy, in General Practice* 670 pp Chicago Year Book Publishers Inc 1940 P 507
- Bleiss H Die Immuntherapie der Warzen und Kondylome *Klin Wchnschr* 11 1071 1025 1932

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTE-MORTEM AND POST-MORTEM RECORDS AS USED  
IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

### CASE 28251

#### PRESENTATION OF CASE

*First admission.* A fifty-five-year-old Italian barber entered the hospital for study.

Three years before entry, he had an attack of "rheumatism," which soon disappeared. One year before admission, he noticed that dribbling occurred after urination and that his urine, which had not changed in appearance, caused itching of the skin of his legs and penis. This was accompanied by nocturia (once a night) but no other symptoms. Rheumatism recurred nine months before admission, and was characterized by intermittent pain and stiffness of the hands, shoulders, knees and left ankle. The symptoms, which were worse in the morning, were occasionally accompanied by swelling of the joints, with questionable reddening, but no incapacitation; they disappeared in six months. Meanwhile, the pruritus increased, was worse at night, and involved the penis, legs, abdomen and arms, but not the hands. No treatment was given, and relief was spontaneous one month before admission. The patient stated that his wife had noticed some pruritus three months before. Six months before entry, the patient lost his initiative and began to tire easily, and three months later noticed that he felt dizzy if he remained on his feet too long. This symptom finally forced him to stop work. One month before admission, he consulted his physician, who found a positive blood Hinton reaction and started treatment two weeks later. During this time, the patient suffered from an increasing thirst, a nocturia of two or three times a night and a steadily increasing sense of fatigue. Two days before admission, he noticed that his stools had become light brown, and a generalized pruritus developed; there was no jaundice. In addition, there were anorexia and postprandial distension. The patient had lost 8 pounds in an unstat ed period, and for the previous three months had had slight epistaxes after blowing his nose.

Thirty-seven years before admission, he had a penile chancre, which was treated locally. The family history was irrelevant.

On examination, the patient was well developed and somewhat undernourished, and the skin was believed to be more deeply pigmented than is usual for his race. The buccal mucous membrane

was pale, and on the right there was a pigmented gray-black area. A generalized lymphadenopathy was present, with small, shotty epitrochlear, cervical, axillary and inguinal lymph nodes. The heart was not enlarged, and there was a soft blowing murmur at the apex. Examination of the lungs was negative. The liver was just palpable, and a firm, nontender spleen was felt four finger-breadths below the costal margin. There was a suggestion of atrophy of the hands, and the left hand, right foot and right knee were tender on motion and pressure.

The temperature, pulse and respirations were normal. The blood pressure was 150 systolic, 70 diastolic, sitting, and 130 systolic, 70 diastolic, standing.

Examination of the urine was negative. The blood showed a red-cell count of 5,530,000 with a hemoglobin of 65 per cent, and a white-cell count of 2800 with 33 per cent polymorphonuclears, 57 per cent lymphocytes, 2 per cent eosinophils and 8 per cent monocytes; the platelets appeared to be normal. The sedimentation rate was 0.48 mm., the serum van den Bergh was normal, and the blood Hinton and Wassermann reactions were positive. A lumbar puncture revealed nothing abnormal, and the spinal-fluid Wassermann reaction was negative. X-ray films of the chest were negative except for an area of calcification in the right infraclavicular region and questionable areas of calcification at the right hilum.

The patient was placed on an arthritic regime and given 5 cc. of Pentnucleotide. During hospitalization, the white-cell count did not rise above 3900, and for this reason it was deemed inadvisable to institute arsenical antisyphilitic treatment. He was discharged three weeks after admission under the care of his physician.

*Second admission* (four years later). A year after discharge, the patient was seen in the Out Patient Department complaining of generalized weakness, fatigue, joint stiffness and "gas on the stomach." Physical examination was negative except for a coarse tremor of the hands and hyperactive knee jerks. A month later, he returned complaining of swelling, tenderness and pain on motion in the hands and ankles, with pain in the hips and back after standing for a long time. Nocturia had increased to four times a night. The joints of the hands, knees and ankles were thickened and stiff, with tenderness on lateral pressure. Tenderness was also present over the sacroiliac joints and lower spine. A search for foci of infection revealed clear sinuses and chronic tonsillitis; the prostate was not enlarged, but moderately tender, and a smear contained many white blood cells. The patient was given a course of prostatic massage, and in a year the urine cleared and the

frequency subsided. Up to this point, he had had only one course of bismuth; two years before admission, the blood Hinton and Wassermann reactions were still positive. A course of neoarsphenamine was started by his physician, but after three treatments the patient complained of upper abdominal distress, gaseous eructations, fatigue, constipation and clay-colored stools; he developed jaundice and a palpable liver, with tenderness in the right hypochondriac region. The red-cell count was 6,430,000, and the white-cell count 6100 with 47 per cent polymorphonuclears, 43 per cent lymphocytes, 6 per cent eosinophils, 3 per cent monocytes and 1 per cent basophils. The patient was seen in the Out Patient Department two weeks later, when jaundice was still present and the liver was just palpable and slightly tender.

Six weeks before admission, the patient contracted a cold followed by a discharging right ear. He was admitted to the Eye and Ear Infirmary, where examination revealed a right otitis media and mastoiditis; culture of the aural discharge yielded hemolytic streptococci. There was a fine nystagmus to the right. An ulceration was present in the left hard palate, with tender, enlarged cervical lymph nodes. The spleen was enlarged and firm and extended almost to the umbilicus, and there was tenderness in the right upper quadrant. The red-cell count was 3,820,000 with a hemoglobin of 61 per cent, and the white-cell count was 3800 with 58 per cent polymorphonuclears and 42 per cent lymphocytes. Repeated lumbar punctures, including spinal-fluid Wassermann reactions, were negative, but a blood Hinton reaction was positive. On the ninth hospital day, a right simple mastoidectomy was performed, and one week later, the patient was transferred to the general hospital. It appeared that six weeks before admission, after five bismuth injections administered by his physician, a few red nonpruritic, slightly raised papules appeared on the flexor surfaces of both arms and spread to involve the legs in the course of the next week. The bismuth was discontinued, but the papules increased in number and appeared on the face. In the preceding few days, the lesions had faded somewhat.

On examination, the patient was wasted and sick. A diffuse, brownish-red, papular eruption, each papule measuring approximately 0.5-cm., was present on the skin of the forearms, palms, buttocks, knees and calves, but no lesions were seen on the mucous membranes. There was a generalized lymphadenopathy. Examination of the heart and lungs was negative. The spleen was palpable 3 cm. below the level of the umbilicus, and the liver one fingerbreadth below the costal

margin. There was some stiffness and limitation of movement in the fingers of the right hand. Examination of the nervous system was negative.

The temperature occasionally rose above normal, the pulse averaged 95, and the respirations were normal. The blood pressure was 120 systolic, 80 diastolic.

Examination of the urine was negative. Examination of the blood showed a red-cell count of 3,800,000 with a hemoglobin of 65 per cent, and a white-cell count of 4200 with 10 per cent polymorphonuclears, 46 per cent lymphocytes, 40 per cent monocytes and 4 per cent eosinophils; the platelets were normal in number. The red cells were microcytic and hypochromic, with much variation in size and shape; no immature cells were found. The sedimentation rate was 0.92 mm., and a hematocrit reading 31.5; the bleeding and clotting times were normal, and an erythrocyte fragility test was normal. The nonprotein nitrogen of the blood serum was 20 mg. and the fasting blood sugar 90 mg. per 100 cc. The serum van den Bergh was normal, a brom-sulfalein test negative, and a formol-gel test positive; the blood vitamin C level was 0.34 mg. per 100 cc., the plasma prothrombin 95.2 per cent, and the antithrombin 117 per cent. Blood Hinton and Wassermann reactions were positive. A tuberculin test was negative with a dilution of 1:10,000; a Congo-red test showed 63 per cent retention in the serum in one hour. Examinations of the stools were negative.

An x-ray film of the chest was negative. The knees were normal; the hands showed tufting of the terminal phalanges and arthritic changes about the joints consistent with rheumatoid arthritis. There was no periostitis to suggest pulmonary osteoarthropathy. A gastrointestinal series showed slight irregularity in the lower end of the esophagus, but varices could not be demonstrated. The stomach was displaced to the right by a lobulated mass, said to be a markedly enlarged spleen. The liver shadow appeared smaller than usual. X-ray study of the pelvis showed evidence of osteoporosis of the visible bones, but no other evidence of disease. There was a slightly fusiform area of calcification projecting into the true pelvis on the left side. Films of the femurs showed a very small area of calcification in the left popliteal space. There was no evidence of Gaucher's disease.

A biopsy of a lymph node showed chronic inflammation and pigmentation. A skin biopsy showed a rather marked perivascular infiltration containing many plasma cells, a picture consistent with parapsoriasis lichenoides.



During hospitalization, the rash gradually faded, and the mastoid incision healed satisfactorily. Frequent slight epistaxes were noticed. The white-cell count varied between 4200 and 1550. One blood film showed 22 per cent polymorphonuclears, 56 per cent lymphocytes, 4 per cent monocytes, 8 per cent eosinophils, 2 per cent basophils and 8 per cent myelocytes; another film showed 4 per cent myelocytes. The patient was discharged one month after admission to the Out Patient Department.

*Final admission* (five months later). The patient returned to the Out Patient Department three months before admission. His strength had returned to a certain degree, but he complained of finger stiffness that was worse in the morning and of inability to flex the fourth and fifth left fingers. Splenomegaly, hepatomegaly and generalized lymphadenopathy were again noted, and there was slight clubbing of the fingers and edema of the legs. The red-cell count was 4,740,000 with a hemoglobin of 72 per cent, and the white-cell count 2600 with 12 per cent polymorphonuclears, 60 per cent lymphocytes, 16 per cent monocytes, 4 per cent eosinophils and 8 per cent basophils; the sedimentation rate was 1.04 mm. The patient was examined again seven weeks later and felt stronger, but showed the same physical findings except for the disappearance of peripheral edema. One month before entry, he was admitted to the Eye and Ear Infirmary complaining of general malaise, anorexia, fever, loss of weight and a mass on the right side of the jaw that had made its appearance five weeks previously. This mass was an abscess and was incised and drained, yielding purulent material that contained hemolytic streptococci and *Staphylococcus aureus*. Another area of redness and swelling that developed below the major abscess was drained, and a biopsy of the surrounding tissue showed chronic inflammation consistent with gumma. The patient was transferred to the general hospital. It appeared that he had had fairly frequent small epistaxes for the previous two years. In the four years of observation, syphilitic treatment had consisted of twenty-two injections of bismuth and nine injections of arsenicals, with mercury and potassium iodide from time to time. Each attempt was hindered by unfavorable systemic reactions, which included jaundice, pruritus, diarrhea and skin reactions. The patient had lost 34 pounds in an unstated period.

On examination, the patient was emaciated but in no discomfort, and the skin showed a more than racial pigmentation. Over the arms and forelegs were several depigmented scars about 1.5 cm. in diameter, with areas of hyperpigmentation over the legs. The right buccal mucous membrane showed an area of deep-brown pigmentation. A

draining sinus with surrounding induration was present in the right neck below the mandible. The scleras appeared slightly icteric. There was a generalized, shotty, painless lymphadenopathy. Examination of the heart and lungs was negative, except for a soft blowing apical systolic murmur. Examination of the abdomen revealed a smooth, firm spleen, which was not tender and reached to one fingerbreadth below the umbilical level. The liver could be palpated one fingerbreadth below the costal margin in the mid-clavicular line and three fingerbreadths below the xiphoid; it was not tender, and the edge was smooth and sharp. Ascites could not be demonstrated. There was clubbing of the fingers and toes, and the patient was unable to flex the right second, third and fourth fingers completely.

The temperature spiked to 101°F., the pulse was 90, and the respirations were normal. The blood pressure was 108 systolic, 70 diastolic.

Examination of the urine showed a ++ test for albumin. Examination of the blood showed a red-cell count of 4,750,000 with a hemoglobin of 65 per cent, and a white-cell count of 1800 with 1 per cent myeloblasts, 0.5 per cent premyelocytes, 2 per cent myelocytes, 7.5 per cent juveniles, 5 per cent band cells, 4.5 per cent segmented polymorphonuclears, 0.5 per cent large lymphocytes, 58 per cent small lymphocytes, 16.5 per cent monocytes, 3 per cent eosinophils, 1.5 per cent basophils, 1 per cent microblasts and 1.5 per cent Turk cells; the platelets appeared normal. A glucose-tolerance test gave a fasting level of 131 mg., in half an hour 188 mg., in one hour 228 mg., and in two hours 123 mg. per 100 cc. A blood Hinton reaction was positive, and a blood culture negative.

The patient continued to run a fever up to 101.6°F., and an area of fluctuant redness developed beneath the large abscess; within two days, the temperature was 104°F., but the white-cell count remained around 2000 despite the administration of Pentnucleotide. On the eleventh hospital day, the abscess was drained, and sternal-marrow and skin biopsies taken. At the end of this procedure, the blood pressure was 80 systolic, 69 diastolic, the pulse 200, and the respirations 40. That night, the patient had a chill, and the next day failed rapidly, developing coarse bubbling rales and wheezes throughout both lungs, with signs of consolidation at the right base, marked dyspnea and cyanosis, and shifting dullness in the abdomen. He died that day, the twelfth after admission, despite supportive measures and two 500-cc. blood transfusions.

A biopsy of the sternal marrow showed a pronounced increase in cellularity, with a preponderance of erythrogenic forms, among which normoblasts predominated, although there were signifi-

ent numbers of erythroblasts. There were increased numbers of eosinophils and no evidence of obstruction of granulocytic maturation. Megakaryocytes were normal in number. The skin biopsy showed chronic inflammation, and although the appearance was not that of gumma, syphilis could not be absolutely ruled out.

### DIFFERENTIAL DIAGNOSIS

DR JOHN H. TALBOTT: There are several diagnoses to be considered in this case. From the duration of symptoms, I think we are justified in assuming that the patient had a serious and chronic malady. The initial complaints of itching, frequency and dribbling suggest the possibility of diabetes mellitus. This supposition is strengthened by the findings of pigmentation, hepatomegaly and splenomegaly, and one might consider hemochromatosis. The glucose tolerance curve showed a delayed response, not unlike that seen in many types of chronic disease. The urine was negative for sugar at all times, however. I do not believe the patient had either diabetes mellitus or hemochromatosis, and I mention them only to discard them. We are cautioned, on the other hand, that liver disease was present. The fact that in arsenical reaction followed the administration of arsenic, even in the absence of jaundice, points toward a hepatitis. Addison's disease and Grucher's disease should be mentioned in passing as improbable causes of the pigmentation. The data regarding the hepatomegaly and the splenomegaly are impressive. The lower edge of the spleen was felt four fingerbreadths below the costal margin and terminally extended below the umbilicus. This was a large spleen such as may be associated with myelogenous leukemia or Banti's disease.

The leukopenia further points to a blood dyscrasia. The white cell count is known to have risen above 5000 on only one occasion during the four year period, following an acute infection. At times, it was as low as 1500, with a marked diminution in polymorphonuclears, an increase in monocytes and, terminally, an increase in myelocytes. The leukopenia did not respond to Pentamidine administration. Several causes are suggested for the leukopenia. The ulcer in the mouth, following an otitis media and mastoiditis, might make one think of agranulocytic angina. This was seen rather often a decade ago, and in many cases was attributed to the ingestion of amidopyrine. Amidopyrine poisoning must be discarded because we have no evidence that the patient ingested any of the material. The sulfonamides may produce a leukopenia, but again there is no history of ingestion. Finally, cirrhosis of the liver is associated with a persistent leukopenia.

The diagnosis of syphilis, I am sure, we must accept. A penile chancre was treated only locally, and persistently positive blood Hinton and Wassermann reactions were reported. The biopsy was consistent with gumma. The postarsenical hepatitis, which was observed on the second admission, four years after the first symptom, might be explained by one of several mechanisms. An arsenical hepatitis may develop in an essentially normal liver as an idiosyncrasy. Secondly, a hepatitis may be superimposed upon a Laennec's cirrhosis of the liver. Finally, a hepatitis may follow the use of arsenicals in a patient with a syphilitic cirrhosis.

The positive formol gel test, an index of increased globulin content of the serum, confirms the impression that some liver disease was present, although the test may be positive in chronic infections, rheumatoid arthritis and syphilis. The Congo red test was not sufficiently positive to justify a supposition of generalized amyloidosis with liver involvement. A normal person should retain at least 80 per cent of the dye in the serum, a typical case of amyloid disease retains less than 20 per cent. The clubbing of the fingers is interesting. There was no x-ray evidence of periostitis to suggest pulmonary osteoarthropathy. Clubbing is present in 10 or 15 per cent of patients with cirrhosis of the liver. I believe in this case we can attribute the clubbing to hepatic cirrhosis. Diffuse pigmentation may also be seen in cirrhosis. The pigmentation may be so extensive as to make the diagnosis of hemochromatosis an academic point.

The increase in size of the left lobe of the liver intrigues me. McCrie and Craven<sup>1</sup> reported several cases of syphilitic hepatitis with predominant regeneration in the left lobe. The statement in the abstract that the right lobe of the liver was below the costal margin and the left lobe was three fingerbreadths below certainly is suggestive of a syphilitic liver.

Disseminated lupus is a possible diagnosis in this case. The skin rash, a frequent finding in lupus, was probably due to bismuth in this patient. The arthritis and perivascular infiltration are seen in lupus. Leukopenia is also seen, but no mention is made of endocarditis, polysclerosis, a persistent anemia or urinary abnormalities. Before seriously considering a diagnosis of disseminated lupus, I think we should have more leading data than we have.

What diagnoses are we willing to make? We have considered and discarded diabetes mellitus, hemochromatosis, disseminated lupus and Addison's disease. I believe that the patient had pneumonia, terminally. I believe that he had syphilis.

pattern, I should agree, was probably normal, although I think that the mucosa was a little too thick—the mucosa and submucosa together. I do not know what causes a short and narrow colon in an infant a few weeks after birth. I remember that we had a case not too long ago in which a baby had a narrow colon. Somebody told me that the Children's Hospital had found narrow colons in cases with cystic fibrosis of the pancreas.

DR. TRACY B. MALLORY: Have you anything further to add, Dr. Garland?

DR. GARLAND: I am afraid I do not know anything more.

DR. MALLORY: As I understand it, your preference is for an underlying infection whose nature you do not know.

DR. GARLAND: On the premise of diarrhea, yes; otherwise, no.

DR. BUTLER: I think it is only fair to say that the physicians at the Children's Hospital who took care of this patient were as puzzled as Dr. Garland, even though they recognized the importance of the autonomic disturbance. Had Dr. Garland seen the child, he would have been more impressed by her vasomotor instability and autonomic imbalance. These were very striking and are hardly appreciated in a reading of the few sentences that relate to them in the written presentation of the case.

DR. WYMAN RICHARDSON: Do infants of this age ever have idiopathic ulcerative colitis?

DR. GARLAND: This patient was very young for it.

#### CLINICAL DIAGNOSES

Chronic nutritional disturbance.

Pneumonia.

Hepatitis, acute, infectious.

#### DR. GARLAND'S DIAGNOSES

Hyperperistalsis, cause unknown.

Terminal infection, with hepatitis.

#### ANATOMICAL DIAGNOSES

Idiopathic ulcerative colitis, with perforation and peritonitis.

Bronchopneumonia, terminal.

Hepatitis and pyelonephritis, mild.

Pancreatic fibrosis (achylia), early.

#### PATHOLOGICAL DISCUSSION

DR. SIDNEY FARBER\*: Not only the physicians who saw this patient but also the pathologists were disturbed. The main clinical working diagnosis was autonomic imbalance. The final discharge diagnosis was chronic nutritional disturbance, underlying etiology undetermined, pneumonia and acute infectious hepatitis. There was a broncho-

pneumonia, particularly of the left upper lobe, but this was of recent origin.

This is the most important finding: in the region of the transverse colon, there was localized peritonitis, some of which was well organized. In addition, there was diffuse peritonitis from which colon bacilli were obtained. The transverse colon proved to be the site of the previous perforation of the bowel. When the bowel was opened, large numbers of ulcers were found involving the transverse colon, descending colon, most markedly, and also the ascending colon and the rectum, less markedly, however. The involvement of the bowel stopped rather abruptly at the ileocecal valve. The gross microscopic picture was characteristic of ulcerative colitis. There was also a diffuse hepatitis, with a considerable amount of inspissation of bile in the biliary canaliculi. Most of the icterus noted was presumably of the obstructive type. There was a very early lesion of the pancreas acini typical of the picture associated with achylia pancreatica. The mucous glands of the trachea and bronchi and some of the glandular structures of the duodenum showed inspissation of mucus and dilatation of the glandular structures. There was infection, a colon bacillus bacteremia. Whatever organisms might have been there before were certainly obscured by this terminal infection. There was some evidence of older infection in the upper respiratory tract, otitis media and slight, healed pyelonephritis. Whatever the cause of this disease may have been, we have not been able to discover it in this case, although we had an ideal opportunity here, since the symptoms began so early after birth. If one compares this picture with a disease somewhat like it, mucous colitis, and if one recalls the stress that Drs. White, Cobb and Jones† and their colleagues have placed on the probable role of the nervous system, a similar direction may be followed here. The tachycardia, the vasomotor instability and the gastrointestinal disturbance may all be grouped together etiologically from that point of view.

I should like to ask Dr. Mallory what he now considers the cause of ulcerative colitis.

DR. MALLORY: If I were to make a guess, it would be along the same general lines—very definitely against a specific infection.

DR. SCHATZKI: How common is this? Is it very rare in babies?

DR. FARBER: In young infants of this age, yes. We have had two under six months in my experience; this one at three months, and one at two.

DR. BUTLER: Did the one at two display this imbalance?

DR. FARBER: Not to such an extent, but in going over the record, one could find evidence of it.

\*Assistant professor of pathology, Harvard Medical School; pathologist, Children's Hospital, Boston.

†White, B. V., Cobb, S., and Jones, C. M. *Mucous Colitis: A psychosomatic medical study of sixty cases*. Psychosomatic Medicine Monograph 1. 103 pp. Washington: National Research Council, 1939.

# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established in 1828

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND  
PUBLISHED UNDER THE JURISDICTION OF THE  
COMMITTEE ON PUBLICATIONS

Official Organ of

THE MASSACHUSETTS MEDICAL SOCIETY  
and

THE NEW HAMPSHIRE MEDICAL SOCIETY

## EDITORIAL BOARD

Joseph Garland, M D	Stephen Rushmore M D
William B. Breed, M D.	Henry R. Viets M D
George R. Minot, M.D.	Robert M. Green M D
Frank H. Lahey, M.D.	Charles C. Lund M D
Shields Warren, M D.	John F. Fulton M D
George L. Tobey, Jr., M D	A. Warren Stearns M D
C. Guy Lane, M D	Dwight O'Hara M D
William A. Rogers, M D	Chester S. Keeler M D

## ASSOCIATE EDITORS

Thomas H. Lanman, M D.	Donald Munro M D
Henry Jackson Jr M D	

Walter P. Bowers, M D., EDITOR EMERITUS  
Robert N. Nye, M D., MANAGING EDITOR  
Clara D. Davies ASSISTANT EDITOR

SUBSCRIPTION TERMS \$600 per year in advance, postage paid for the United States (medical students, \$3 50 per year), Canada \$7 04 per year, Boston funds, \$8 52 per year for all foreign countries belonging to the Postal Union

MATERIAL for early publication should be received not later than noon on Friday

THE JOURNAL does not hold itself responsible for statements made by any contributor

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston, Massachusetts

## MASSACHUSETTS LICENSES GENERAL HOSPITALS

UNDER the provisions of Chapter 661 of the Acts of 1941, the Massachusetts Department of Public Health has promulgated rules and regulations for the licensing of general hospitals and sanatoriums in Massachusetts, which appear elsewhere in this issue of the *Journal*. Although only two other states, Connecticut and Minnesota, have accepted the licensing of general hospitals as a public function, the principle is by no means new in Massachusetts. As early as 1867, the State Department of Public Welfare was authorized to issue a "license to any person it deems suitable to establish and keep a maternity hospital or ward or other place for the reception, care and treatment of women

during pregnancy or delivery." This action was followed in 1909 by the licensing by the Department of Mental Health of private hospitals for patients with mental diseases.

In spite of this recognition of the public interest in hospitals and in the standards of hospital care, it has, up to the present time, been possible for any person, lay or medical, to establish and maintain a general hospital anywhere in Massachusetts if his application was approved by the selectmen or board of aldermen of the town or city in question. The voluntary supervision of hospitals that has been carried on for many years by the American College of Surgeons and the American Medical Association has been of the greatest value in bringing the standards of hospital care to their present high level but is, of course, effective only in the institutions that choose to avail themselves of it. The Massachusetts Medical Society and the Massachusetts Hospital Association, by their support of this bill, have expressed the opinion that the citizens of Massachusetts are entitled to the assurance that all hospitals, on which they depend for the most vital part of their medical care, meet the generally accepted professional standards of service.

It is not the object of the licensing act or the intention of the regulations adopted thereunder to tell the physicians of Massachusetts what they may or may not do in hospitals but rather to ensure that the practice of medicine in hospitals is carried on in suitable quarters with the aid of properly trained assistants, with adequate equipment and with such laboratory and other auxiliary services as are recognized as essential to modern hospital care. For the further protection of patients, the hospital records must be sufficiently complete to make clear the diagnosis and to show how it is established, and to describe concisely the treatment given, including the type of operation and operative findings. The value of such records to physician and patient alike is universally recognized in professional circles, and adequate medical records have been a major factor in the improve-

ment of hospital services during the past fifty years.

The detailed requirements for maternity hospitals and nurseries may seem unnecessarily exacting to the generation of practitioners who have been accustomed to think of obstetrics as a routine part of general practice. The Massachusetts standards, however, are substantially less exacting than the widely commended maternity-hospital regulations of New York City and of Chicago. Although recognizing the limitations of small hospitals in meeting optimum modern requirements, the new state regulations definitely reflect the recent attempts of the Massachusetts Medical Society and the Department of Public Health to throw every reasonable safeguard around childbirth and further to reduce the excessive maternal mortality rate.

This assumption of responsibility for minimal standards of hospital service by an official agency does not constitute "state medicine." Under the provisions of this act and the adopted regulations, all licensed physicians are free to practise in hospitals in accordance with the accepted standards of their own professional organizations. Hospital licensing on this basis is simply a recognition of the citizens' interest in what has become an essential public service.

---

#### MEDICAL BIBLIOGRAPHY OF SIXTEENTH-CENTURY AUTHORS

SOON after printing began, five hundred years ago, interest was shown in books by medical authors. So far as is known, the first book printed of an exclusively medical nature was published in 1471. In the next ten years, however, over two hundred such books appeared, as listed by Osler in *Incunabula Medica* (Oxford, 1923). Many collections of these items from the early presses are known, the most extensive in America being at the Boston Medical Library. Each book in this section of medical literature has been studied meticulously by various scholars, and even with works issued without title page, date, place or printer, experts such as Dr. Arnold C. Klebs

are able to supply most of the missing data. It seems probable that no group of objects ever devised by man has received so much attention from the learned world. The work still goes on: Klebs's standard short title list, *Incunabula Scientifica et Medica* (Bruges, 1938), is being constantly checked and even augmented; and Miss Margaret B. Stillwell, of Brown University, has only recently completed *Incunabula in American Libraries: A second census of fifteenth-century books owned in the United States, Mexico and Canada* (New York, 1940).

In view of all the work that has been done on fifteenth-century books, it is surprising how little attention has been paid to those published during the sixteenth century. Most libraries, for instance, have isolated their incunabula, but leave the sixteenth-century books in the stacks, sometimes not realizing that these are as precious and rare as many published in the preceding century. Gradual interest in this group of books, and in the larger list of all items published by persons living in the sixteenth century, has resulted in the issue of the first fasciculus of *Bio-bibliography of XVI. Century Medical Authors* (Washington, 1941), by Claudius F. Mayer, the learned editor of the *Index-Catalogue of the Surgeon General's Library*.

In Dr. Mayer's list will be found many unusual features. Its accuracy and completeness, based on the great collections in the Army Medical Library, are assured. In addition to the usual features in a bibliographic list, one will find the location of known copies of individual books, not only in this country, but abroad. Doubtful or nonexistent copies are referred to, and in most cases a brief biographic notice is given of the author, with a reproduction of his portrait.

This project, now only part way through the letter "A," is a welcome addition to bio-bibliographic reference, particularly so in view of the fact that copies of books known to exist in America are referred to, and the essential facts regarding the authors are given. No one is better equipped than Dr. Mayer to carry out this long-needed work,

and he is to be congratulated on the completion of the first section. Plans have been made to issue the fasciculi regularly, the entire work will take several years.

## MEDICAL EPONYM

### PICK'S DISEASE

Dr Friedel Pick (1867-1926), first assistant in the First German Medical Clinic at Prague, presented a discussion, "Über chronische, unter dem Bilde der Lebercirrhose verlaufende Pericarditis (pericarditische Pseudohepaticirrhose) nebst Bemerkungen über die Zuckergussleber (Curschmann) [Chronic Pericarditis—Pericarditic Pseudocirrhosis of the Liver—Simulating the Course of Cirrhosis of the Liver, with Observations on the Frosted Liver (Curschmann)]," in the *Zeitschrift für klinische Medizin* (29:385-410, 1896). A portion of the translation follows:

There is a symptom complex (pericarditic pseudo-cirrhosis of the liver) that simulates one of the mixed forms of cirrhosis of the liver (enlarged liver, marked ascites without jaundice). This results from disturbances in the circulation of the liver caused by a latent pericarditis. These lead to an overgrowth of connective tissue, which produces marked ascites by causing congestion in the portal circulation.

The condition usually occurs in young persons but may be seen in later life.

The following points are to be considered in the differential diagnosis: absence of any etiologic agent for cirrhosis of the liver, a history indicating a previous pericarditis and a previous edema of the legs. Only careful examination of the heart can finally establish the diagnosis.

R W B

## MASSACHUSETTS MEDICAL SOCIETY

### COMMITTEE ON MATERNAL WELFARE

#### CASE HISTORY FATAL ECLAMPSIA AND CEREBRAL HEMORRHAGE

A twenty-three year-old primipara was first seen during the seventh month of pregnancy, when she had a blood pressure of 160 systolic, 94 diastolic. Her care from this time on was adequate if not intelligent; she was hospitalized for the remaining weeks of pregnancy. Physical examination on entry was essentially negative, and the past history showed no serious illnesses or operations. Albuminuria did not appear until the thirty-fourth week. The usual pre-eclamptic and toxemic treatment was instituted. The patient did not go into labor until three weeks after the expected date, and the systolic blood pressure ranged from 150

to 160 for the last two weeks, when albuminuria was also constant. After four and a half hours of spontaneous labor, she developed eclampsia accompanied by a cerebral hemorrhage from which she died very shortly. A post mortem cesarean section was performed, but the baby did not live. Autopsy revealed massive cerebral hemorrhage, with signs typical of eclampsia in the liver and kidneys.

**Comment.** There is no excuse for this fatality. Any patient under constant observation for two months who runs a constantly elevated blood pressure and albuminuria should not develop eclampsia and die of cerebral hemorrhage. Although the systolic blood pressure is not recorded as having risen above 160, it is very likely that it did, since it is extremely uncommon for a patient with a systolic blood pressure no higher than this to have a convulsion and fatal cerebral hemorrhage. Patients with toxemia who show a systolic blood pressure of over 150 constantly accompanied by albuminuria when they are in the eighth month of pregnancy, and do not improve with treatment become problems for induction, since kidney damage is undoubtedly progressing. A sharp rise in blood pressure or a diminution in the urinary output calls for immediate delivery. If the cervix is unfavorable for induction, cesarean section is the operation of choice. Depending on the condition of the cervix, either one or the other should have been performed at least two weeks before this patient died.

Post mortem cesarean sections are a moot question. In this case, as so often happens, nothing was accomplished. It is very gratifying that an autopsy was performed. It tells the true cause of the fatality.

### DEATHS

**BUTLER**—FRANCIS J. BUTLER, MD, of Worcester, died June 7. He was in his sixtieth year.

Dr Butler received his degree from Georgetown University School of Medicine in 1908. He was a member of the staffs of St. Vincent and Worcester Hahnemann hospitals and was a fellow of the Massachusetts Medical Society and the American Medical Association.

**COX**—STANLEY C. COX, MD, of Holyoke, died June 7. He was in his sixtieth year.

Born in South Hadley Falls, Dr Cox received his degree from University of Michigan Medical School in 1910. For twenty-one years he served as associate medical examiner and medical examiner for the third district of Hampden County. He was head of the local Medical Division of the Massachusetts Committee on Public Safety in Holyoke. He was a member of the American College of Physicians and Surgeons and a fellow of the Massachusetts Medical Society and the American Medical Association.

His widow, two sons, three daughters, two brothers and a sister survive him.

**WILLIAMS**—**DAVID L. WILLIAMS, M.D.**, of Winthrop, died June 7. He was in his sixty-seventh year.

Born in South Boston, Dr. Williams received his degree from Tufts College Medical School in 1906. He was a former member of the staffs of Harvard and Tufts College medical schools. From 1936 to 1938, he was state commissioner of mental diseases. He was a former member of the Massachusetts Medical Society and the American Medical Association.

His widow, two sons, two daughters and a brother survive him.

## WAR ACTIVITIES

### CIVILIAN DEFENSE

#### CLARIFICATION OF FUNCTION OF RED CROSS AND CIVILIAN DEFENSE UNITS

The following joint statement concerning the respective authority and responsibilities of the local Red Cross chapters and the local Civilian Defense councils was issued on May 18, 1942:

To secure unity of effort and avoid duplication of facilities in meeting civilian needs arising from enemy action, this statement is issued by the Office of Civilian Defense and the American National Red Cross for the guidance of defense councils and Red Cross chapters.

It is the responsibility of local defense councils to see that adequate provision is made for all services required in the event of bombing or other enemy attack. During an emergency period, the commander of the Citizens' Defense Corps will exercise control over all such services.

With respect to emergency medical services and emergency feeding, housing and clothing, provision should be made in each community in conformity with the following principles:

#### EMERGENCY MEDICAL SERVICES

During bombing or other enemy attack, all services are directed from the control center in charge of the commander of the Citizens' Defense Corps. Responsibility for the care of those injured as a result of enemy action rests with the Emergency Medical Service of the Citizens' Defense Corps under the direction of the chief of the Emergency Medical Service.

Red Cross chapters assist the Emergency Medical Service by (a) recruiting and training volunteer nurses' aides, who will be utilized by the Emergency Medical Service at base and casualty hospitals, casualty stations and first-aid posts; (b) furnishing lists of persons trained in first aid to be enlisted by the Emergency Medical Service as members of its stretcher teams; (c) providing dressings, bandages and supplementary equipment as the chapter may decide in consultation with the chief of Emergency Medical Service; (d) equipping and operating emergency ambulances to be assigned to the Emergency Medical Service and to serve under its direction; (e) providing supplementary transportation for walking injured and for Emergency Medical Service personnel. During the emergency period, ambulances and motor units assigned to such transportation service will be under the direction of the chief of Emergency Medical Service or the trans-

port officer. The Emergency Medical Service of the Office of Civilian Defense will not be duplicated by the Red Cross but will be utilized by the Red Cross in natural disasters.

#### EMERGENCY FEEDING, HOUSING AND CLOTHING

In the joint statement, dated April 17, 1942, of the Office of Defense Health and Welfare Services and the American Red Cross it is agreed: "With respect to the emergency period during which special facilities must be made available to meet emergency needs without notice, the Federal Security Administrator will look to the local facilities and resources of the American Red Cross to provide food, clothing and temporary shelter." These services will be provided locally during an emergency period by the Red Cross under the control of the commander of the Citizens' Defense Corps in accordance with detailed plans to be worked out jointly by the commander, the Red Cross chapter and the public-welfare authority.

Defense councils should avoid duplication of these facilities. Where an emergency food and housing corps has already been organized and equipped to the satisfaction of the commander of the Citizens' Defense Corps, its function should be co-ordinated with the functions of the public-welfare authorities and the Red Cross chapter and, if possible, consolidated.

After the emergency period, the appropriate public agencies are expected to undertake the care of civilians in accordance with plans developed in conjunction with the Office of Defense Health and Welfare Services and the Federal Security Administrator. Funds will be made available for this purpose by the federal government through the Federal Security Administrator. Local welfare agencies and Red Cross chapters should be guided in their relations by the agreement signed on April 17, 1942, by the Office of Defense Health and Welfare Service and the American Red Cross.

All Red Cross volunteers enlisted in the emergency feeding and housing service, and all other Red Cross volunteers who are to be in service during and following bombing or other enemy action, will register with the local Civilian Defense volunteer office. The cards of all such registrants are to be marked so as to show that these volunteers are in Red Cross service. In order to obtain necessary freedom of movement during and immediately after enemy action, Red Cross personnel certified to the commander by the chapter for emergency feeding, housing and clothing services will be furnished with identification cards issued to Citizens' Defense Corps personnel and will be authorized to wear the official armband.

This statement supersedes the joint statements of September 4 and December 22, 1941.

NORMAN H. DAVIS, *Chairman*  
American Red Cross

JAMES M. LANDIS, *Director*  
Office of Civilian Defense

## MISCELLANY

### PROMIN IN THE TREATMENT OF TUBERCULOSIS

Success in the use of chemotherapeutic agents in combating infectious diseases revived the hope that eventually a substance will be found that will be useful clinically in the treatment of tuberculosis. Promin, one of the compounds used experimentally, has already been discussed

in the public press. A recent article (Feldman, W. H. Hinshaw, H. C., and Moses, H. E. Promin in experimental tuberculosis. *Am Rev Tuberc* 45 303-333, 1942) summarizes the results obtained in animals with this chemical.

In 1938, sulfanilamide was reported to have an inhibitory effect on the development of experimental tuberculosis in guinea pigs, but subsequent papers held out scant hope that this agent would prove to be a specific remedy for tuberculosis in human beings.

Promin, in its solid form, varies from white to light yellow and is slightly hygroscopic. It is highly soluble in water, and 40 per cent solutions are stable indefinitely and may be sterilized by heat. It is slightly bitter but small amounts may be mixed with the food of animals without impairing their appetite or digestion. Guinea pigs tolerate 1 per cent promin in their foods and will consume from 300 to 400 mg of the drug per twenty-four hours. Increasing the concentration of promin to 2 per cent causes anorexia which interferes with the quantity of food taken.

In the first experiment promin to the amount of 1 per cent was added to the food of 30 guinea pigs. 20 others received the same diet except for promin. Two days after the feeding experiment began all guinea pigs were inoculated subcutaneously with human tubercle bacilli of known strain. On the eighty-fourth day all the animals in the control group had died and 24 of the animals that had received promin were living. Promin was then removed from the diet of 12 of the survivors. After eighty-two more days 13 animals still lived 5 of which had received promin for the entire period (one hundred and sixty-six days) and the other 8 for the first period of eighty-four days only. The purpose of this procedure was to determine if latent tuberculosis would become reactivated when treatment was discontinued.

The value of a chemotherapeutic agent must be appraised not only on survival time, but also on the character of the disease process. With one exception the degree of tuberculous involvement in the animals that received promin was notably less than that in the controls.

Although the results indicated that in many of the animals promin had either prevented the establishment of lesions or caused their eventual disappearance, another effect of the drug which is perhaps of more importance was that exerted on the cellular elements of the lesions. In the vast majority of the animals in the treated group that had lesions the histologic characteristics of the pathologic process apparently were modified favorably. This was especially true of the lesions in the parenchymal tissues. The lesions were usually small and discrete and the epithelioid phase of the reactive process predominated. Necrosis was infrequent, and a tendency of the process toward fibrosis was frequently observed. These features of the morbid process were in marked contrast to those that characterized the disease in the control group of animals. In the latter, the disease was extensive, destructive and progressive.

The objectives of the second experiment were to confirm the results of the first and to determine what effect if any promin might have on a tuberculous infection introduced at the same time as or at varying periods before treatment with promin was begun.

Fifty guinea pigs were selected and divided into eight groups. Group I consisted of 12 animals infected but not treated (controls). Group VIII consisted of 20 animals whose treatment began two days prior to infection. Groups II to VII each contained 8 animals and treatment was begun in relation to the day of infection at various intervals as follows: Group II on the day of infection; Group III after three days; Group IV, after one

week; Group V, after two weeks; Group VI, after four weeks; and Group VII, after six weeks.

All animals except I reacted to tuberculin. Generally speaking the reactions of the animals that received promin were less severe than those of the untreated animals.

Although the general physical condition of the animals remained satisfactory, changes indicative of toxic manifestations were noted in the blood and spleen. Studies as yet incomplete indicate that in guinea pigs, promin may induce a hemolytic type of anemia but with adequate regeneration as indicated by a corresponding reticulocytosis.

The difference in survival times of the several groups was striking. When the last of the untreated animals died one hundred and eighty-nine days after inoculation, 94 per cent of the treated animals were still living. Of the treated animals that died none had sufficient tuberculosis to account for death, and this percentage of deaths might reasonably be considered an average or normal mortality rate for guinea pigs.

Examination of the tissues and organs of the animals showed that all untreated animals were tuberculous; that in 57 per cent of the treated animals no evidence of infection in the visceral organs was found, that, in the remainder of those treated tuberculosis was found (with a few exceptions) of minimal severity, and that 43 per cent of the treated animals failed to show evidence of disseminated tuberculosis.

The failure to demonstrate lesions of tuberculosis in a considerable number of the animals that were treated and the fact that the disease in the treated animals was with few exceptions minimal and nonprogressive indicate that the action of the drug was significant. That fairly comparable results occurred in the treated animals, regardless of whether the administration of the drug was started before or as long as four or six weeks after inoculation with tubercle bacilli was surprising and must indicate that the drug was effectively operative against a tuberculous infection in which morbid changes already were established when administration of the drug was started.

The conclusion of the two experiments is that promin has a deterrent effect on experimental tuberculous infection.

Encouraged by these carefully controlled animal experiments workers have cautiously used promin in the treatment of a few cases of tuberculosis in human beings. Administration of the drug has proved difficult since its toxic effect in man is found to be much higher than that in the guinea pig. In certain cases it has been found necessary to discontinue treatment because of unfavorable symptoms attributed to the drug itself. In other cases in which treatment has been prolonged (five months or more) results thus far show varying effects. In a few definitely demonstrable improvement occurs in others little or no change is observed. In some patients the disease goes on developing progressively, with no apparent effect from the treatment.

It is obvious that a freshly infected guinea pig presents a very different pathologic picture from that of a well-developed human case with destruction of tissue and extensive fibrosis interfering with access of the drug to living tubercle bacilli.

Despite the present lack of convincing evidence of promin's value in the treatment of human tuberculosis there is a definite belief that further trial in skilled hands is indicated. — Reprinted from *Tuberculosis Abstracts* June, 1942.



## THE BEGG SOCIETY

A medical-discussion group, to be known as The Begg Society, has been formed at Boston University School of Medicine in honor of the late Dr. Alexander S. Begg, dean of the school for seventeen years. An annual prize will be offered to the student author of the best scientific paper submitted by a member of the society. Dr. Chester S. Keefer was elected president by the students, and Drs. Joseph F. Ross and Francis M. Forster were named to the prize committee.

## NOTE

At the recent annual meeting of the American Gastro-Enterological Association, held in Atlantic City, Dr. Sara M. Jordan, of Boston, was elected president for the ensuing year.

## CORRESPONDENCE

### REFUGEE PHYSICIANS

*To the Editor:* The Greater Lawrence Medical Association has always been able to handle its local problems, but now we are confronted with a situation that is statewide; and we appeal to the Massachusetts Medical Society for its solution.

Massachusetts has had the reputation for being a "dumping ground" for physicians not wanted elsewhere; once again we have that undesirable distinction, as evidenced by the influx of alien physicians in this state. No doubt the Board of Registration in Medicine is being swamped with their applications.

All the eligible members of our organization have volunteered their services either to the armed forces or to federal services through the Procurement and Assignment Forms. We are ready to sacrifice everything for our country; yet, is it Americanism to penalize us with the thought that our patients, whom we have served with the best of our ability with honest medicine, should suddenly be left to the mercy of ignorant and incompetent alien doctors?

There are over 200 refugee doctors practicing in Massachusetts; and there will be many, many more unless something is done quickly. Recently, we raised the standards of certain unrecognized schools; yet we allow these refugee physicians in Massachusetts, whose class of school and educational background cannot be verified by the examining board.

Major Seeley does not want these men to treat our boys in the army; yet, they are allowed to go into private practice in this hour of trial, when it is essential that the morale of our people be kept at the highest level possible.

Twenty-eight States, either by statute or by a ruling of the examining board, require full citizenship for medical licensure. The Greater Lawrence Medical Association believes that this requisition should be put into immediate effect by the State Board of Registration in Medicine. Within the five-year period required for full citizenship, the alien physician can acquire our ideals, our ethics, and the American way of practicing medicine. Most important of all, this would leave no loopholes for spies, saboteurs or subversive activities. Is this expecting too much from anyone who found existence in another land unbearable? Let us not forget that we are a nation at war.

PHILIP E. ZANFAGNA, *President*

Greater Lawrence Medical Association

126 Haverhill Street  
Lawrence, Massachusetts

## RULES AND REGULATIONS FOR LICENSING HOSPITALS

### HOSPITAL STANDARDS

*To the Editor:* The following are the rules and regulations established under the authority of Chapter 11 Sections 71 to 73 inclusive (Tercentenary Edition), as amended by Chapter 661, Acts of 1941, for the licensing of hospitals and sanatoriums by the Department of Public Health.

These rules and regulations were approved and adopted at a meeting of the Department of Public Health on April 14, 1942.

PAUL J. JAKMAU, M.I.  
*Commissioner of Public Health*

State House  
Boston

\* \* \*

## RULES AND REGULATIONS FOR THE LICENSING OF HOSPITALS BY THE MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### I. INTRODUCTION

#### A. *Legal authority.*

- Chapter III of the General Laws (Tercentenary Edition) as amended by Chapter 661 of the Acts of 1941 authorizes the Department of Public Health to issue for a term of two years a license, subject to revocation by it for cause, to any person whom it deems suitable and responsible to establish and maintain a hospital or sanatorium which meets the requirements of the department established in accordance with its rules and regulations. The act also provides for the transfer of licensing of maternity hospitals and maternity wards from the Department of Public Welfare to the Department of Public Health.
- As a guide in carrying out this responsibility the department, in accordance with authority granted in Section 72 of the above Act, has adopted the following rules and regulations.

#### B. *Definitions.*

- Under the provisions of this act a hospital or sanatorium is defined as any institution, whether conducted for charity or for profit, which is advertised, announced or maintained for the expressed or implied purpose of caring for persons admitted thereto for purposes of diagnosis or medical or surgical treatment which is rendered within said institution.
- The term "maternity hospital" shall mean any hospital institution or place other than the home of a near relative in which pregnant women are cared for or delivered; the term "newborn nursery" shall mean any room, rooms or ward in such hospital, institution or place in which newborn babies are cared for or are treated.
- The term "department" as used in these regulations shall mean the Massachusetts Department of Public Health.
- Institutions not included in the provisions of the act are those caring for cases of mental diseases and licensed by the Department of Mental Health, including nervous diseases. It does not include convalescent homes or homes for the aged, dispensaries or clinics.

**C. Issuance of license**

- 1 Application for a hospital license must be made in writing upon a form provided by the department. It shall contain the name of the applicant or if an association or corporation the names of any two officers thereof, the name of the hospital, the total bed capacity of the hospital, and in Groups A and B, the number of beds for patients on each floor, the type of hospital to be operated, the location thereof and the name of the person in charge. The license fee of \$1000, payable to the Commonwealth of Massachusetts, must accompany the application.
- 2 The applicant must be a person of reputable character and shall provide references satisfactory to the department.
- 3 Every hospital shall be designated a permanent and distinctive name which shall appear on the application for license, and which shall not be changed without first notifying the department.
- 4 Applications for a license to establish or maintain a hospital or sanatorium shall be considered by the department only if the local board of health has first certified to the department that, from its inspection and examination of said proposed hospital or sanatorium, it is suitable for the purpose.
- 5 The license must be conspicuously posted on the premises.

**D. Revocation of license** A hospital license may be revoked by the department on any of the following grounds, subject to Section 1, Chapter 661, of the Acts of 1941

- 1 Violation of the provisions of the licensing act or of the standards, rules or regulations of the department adopted thereunder.
- 2 Permitting, aiding or abetting the commission of any illegal act in such institution.

Each license shall be returned immediately to the department on its expiration or revocation.

**E. Classification of institutions** For the purpose of these regulations, all institutions licensed under the provisions of this act are classified as follows

- 1 General hospitals with maternity service
- 2 General hospitals without maternity service
- 3 Maternity hospitals
- 4 Tuberculosis hospitals
- 5 Other types of hospitals designated

Hospitals as above classified are divided into the following groups: Group A, 1 to 49 beds, Group B, 50 to 149 beds, Group C, 150 or more beds.

**II. GENERAL REGULATIONS****A. Fire protection** Provisions for fire protection and egress shall be satisfactory to the hospital supervisor of the department and to an inspector of the Massachusetts Department of Public Safety.**B. Sanitation** No system of water supply, sewerage or garbage disposal shall be installed, nor shall such existing system be materially altered or extended until complete plans and specifications have been submitted to and approved by the department. Any existing system of water supply, sewerage or

refuse disposal must meet the requirements for hospitals as established by the department. All construction of such systems must be carried out in accordance with the plans approved by the department.

- 1 **Water supply** The water supply must be of safe, sanitary quality and obtained from a water supply system approved by the department. Running hot and cold water shall be available on each floor of the hospital.
- 2 **Sewage disposal** Sewage shall be discharged into a municipal sewerage system where such a system is available; otherwise, the sewage shall be collected and disposed of in a manner approved by the department.
- 3 **Plumbing** Toilet facilities shall be provided in accordance with the size and number of beds of the hospital. Plumbing drainage and other arrangements for disposal of excreta, and infectious discharges and institutional wastes shall be in accordance with the standards established by Chapter 302, Acts of 1938, for plumbing in buildings owned and used by the Commonwealth.
- 4 **Waste disposal** All organic waste matter resulting from surgical or medical treatment shall be disposed of by incineration. All other refuse shall be stored and removed from the premises in a manner which does not create a nuisance.
- 5 **Garbage disposal** Suitable facilities shall be provided for collection and disposal of garbage at frequent intervals in a manner which does not create a nuisance.
- 6 **Screens** All outside doors, windows and other outside openings shall be screened against flies and mosquitoes, and proper protection provided against vermin.

**C. Heating** Heating plant shall be adequate to maintain a cold weather temperature of 70°F in all rooms used by patients.**D. Lighting**

- 1 Each patient's room should be an outside room with a satisfactory amount of natural light. The window area shall be not less than one eighth of the floor area. All service rooms and working centers shall be adequately lighted. Hallways not otherwise satisfactorily illuminated shall be provided with artificial light giving sufficient illumination to visualize clearly stairways and exits of said halls night and day.
- 2 All permanent electric installation shall comply with the National Electric Code of the National Board of Fire Underwriters and state and local building regulations.
- 3 Emergency lighting facilities must be provided for operating suites and emergency rooms as a storage battery system or battery operated lamps.

**E. Ventilation** Buildings shall be at all times adequately ventilated. Kitchen, bathrooms and service rooms shall be so located and ventilated as to prevent offensive odors from entering patients' rooms and public hallways.**F. Kitchen and food handling** The kitchen, storeroom and other rooms where food or materials used in the preparation of food are stored, exposed or

handled in the process of preparation or consumption shall be in a clean and sanitary condition, and protected from contamination of any kind. Kitchen facilities shall include refrigeration, and perishable goods must be kept at a temperature low enough to prevent deterioration.

G. *Laundry.* The institution shall be equipped with the necessary laundry facilities for the proper cleansing of linen and other washable goods, or satisfactory arrangement be made for such cleansing in a commercial laundry.

H. *Rooms and wards.*

1. Except for nurseries and children's wards, rooms shall be of sufficient size to allow not less than 50 square feet of floor space per bed, and at least 3 feet between beds.
2. Screens shall be provided in wards or multiple bed-rooms in order to secure privacy for each patient. Permanent bed curtains are desirable.

I. *Equipment and furnishings.*

1. There shall be satisfactory provision for the care of clothing, toilet articles and other personal belongings of the patients.
2. A sufficient supply of clean bedding, bed linen, towels and other supplies shall be available for use at all times.
3. There shall be sufficient equipment for nursing care according to type of patients accepted by the institution.
4. Means for signaling nurses must be provided within easy reach of patients confined to bed.
5. Adequate facilities shall be provided for hand washing for personnel.
6. Proper sterilizing equipment shall be provided in accordance with the needs of the type of patients treated.
7. Adequate toilet and bathing facilities shall be provided on each floor in accordance with the standards of the department.
8. There shall be a utility sink on each floor of the hospital.
9. There shall be satisfactory facilities in the utility room for the disposal of contents of the urinals and bed pans, and for cleansing of the same.

J. *Laboratory facilities.* Hospitals in Group A shall provide laboratory facilities for performing routine chemical and microscopic examinations of the urine and complete blood counts. Such clinical laboratory facilities should be under supervision of an experienced clinical pathologist. Such hospitals shall also regularly utilize the services of an experienced clinical pathologist or an approved laboratory for complete clinical, hematological, bacteriological and chemical examinations, as indicated.

Hospitals in Groups B and C shall have a laboratory capable of making the standard hematological, bacteriological, pathological and chemical diagnostic examinations under the supervision of a competent pathologist, or have regular arrangements for obtaining all such services from an approved laboratory.

All abnormal tissues removed at operation, except tonsils and adenoids, shall be examined by the pathologist and a report thereon entered in the patient's record.

K. *X-ray.*

1. Hospitals in Group A which maintain a medical or surgical service shall provide at least a shock-proof portable x-ray machine under the supervision of a competent medical roentgenologist.
2. Hospitals in Groups B and C shall have x-ray equipment capable of performing standard diagnostic roentgenological examinations, such as gastrointestinal series, gall-bladder examinations, chest films and so forth, under the direction of a competent medical roentgenologist. A fluoroscopic unit shall be included.

L. *Drugs.* Drugs, poisons, stimulants and medicines shall be plainly labeled and securely locked in a cabinet, closet or separate room, accessible only to the physician or nurse in charge.

M. *Personnel.*

1. There shall be a competent, well-trained executive officer or administrator with authority and responsibility to carry out the policies of the hospital as authorized by the governing board or owner.
2. There shall be a staff of physicians and surgeons licensed to practice medicine in the Commonwealth of Massachusetts. This staff shall be organized with a chief of staff or medical director. Hospitals of Groups B and C shall be so organized that there shall be a responsible head of each department. There shall be an advisory group of recognized consultants in the fields of medicine covered by the hospital.
3. There shall be a set of by-laws, rules and regulations which are approved by the medical staff, signed by the chairman and secretary and approved by the governing board or owner.
4. There shall be a superintendent of nurses who is a registered nurse, and there shall be at all times at least one registered nurse on duty.
5. The operating room and delivery room shall be under the supervision of registered nurses.
6. The ratio of nursing staff to patients shall be adequate for satisfactory care of the patients.
7. All hospitals shall have a registered physician available on call at all times. (On account of war conditions it is not possible to set up a definite requirement in regard to resident physicians at this time.)

N. *Medical records.*

1. The hospital shall keep complete and accurate records of each patient from the time of admission to the time of discharge. Such patient records shall include: adequate identification data; family, personal, past and present illness history; physical examinations; reports of special examinations, including reports of clinical and pathological laboratory findings and x-ray findings; records of consultations; provisional diagnosis; reports of anesthesia and surgical operations performed; treatment notes and progress notes; temperature, pulse and respiration charts; final diagnosis and discharge note, signed by the physician.
2. In case of autopsy, a copy of the autopsy protocol shall be attached to the record.
3. All notes shall be legibly written or typed and signed.

- 4 A complete list of all births and deaths occurring in the institution shall be sent to the clerk of the town in which the hospital is located, within the first five days of the following month, in accordance with the provisions of Section 6, Chapter 46 of the General Laws
- 5 A summary annual report of the activities of the hospital on forms provided by the department shall be filed with the department within three months of termination of each calendar year
- 6 The following additional records shall be kept in a form and manner prescribed by or acceptable to the department: record of admissions, register of deaths, daily census record, clinical records, narcotic registers of records, records of physicians' orders, autopsy protocols

### III REGULATIONS FOR SURGICAL DEPARTMENT

In addition to the general regulations all hospitals in which surgical operations other than emergency operations are performed shall conform to the following regulations

A. *Operating room* The operating room shall have impervious floor and washable walls. There shall be a satisfactory means of illumination of the operative field as well as general illumination. There shall be facilities for scrubbing preferably in a separate room, with running hot and cold water delivered through spray faucets and controlable without use of the hands. Heating shall be adequate to maintain a temperature of 60°F in the operating room. A suction apparatus shall be available.

B. *Surgical equipment* The hospital shall constantly have on hand sufficient instruments to perform an abdominal operation and a supply of sterile dressings and linen. There shall be an operating table so built that it can easily be placed in lithotomy or in Trendelenburg position with the patient on the table.

C. *Sterilization* The equipment shall include an autoclave capable of operation under 15 pounds steam pressure and a boiling water sterilizer. An acceptable aseptic technic shall be observed in all major or minor operative procedures. Proper care shall be taken to prevent contamination of the surgical field, sterile tables or operating team by visitors. Likewise, after an operation on a septic case the operating room shall be thoroughly cleansed in a manner adequate for the type of contamination existing.

D. *Anesthesia* There shall be satisfactory equipment to allow the administration of nitrous oxide, oxygen and carbon dioxide. In operating rooms using anesthetic gases capable of exploding under certain conditions of concentration, humidity and so forth, all reasonable precautions shall be taken to avoid this hazard.

E. *Staff* Surgical operations shall be done only by physicians designated by the hospital as qualified to do surgery.

F. *Preoperative care* Operations under a general anesthetic (inhalation, spinal, intravenous or rectal) shall not be performed nor a general anesthetic given until the patient has had a physical exam-

ination including examination of the chest for respiratory infection or cardiac disease and including a urinalysis with tests for albumin and sugar. The results of these examinations, together with the preoperative diagnosis, shall be entered in the patient's record.

G. *Operative records* An accurate and complete description of the technic of operation and the findings, and a statement of organs or tissues removed, together with the postoperative diagnosis, shall be entered by the surgeon in the patient's record immediately following the operation.

H. *Postoperative care* After the administration of a general or spinal anesthetic, patients shall be constantly attended by a nurse until they have regained consciousness or until the effects of the anesthetic have worn off. After any major operation, adequate nursing services shall be provided so that patients are closely watched and given all necessary care.

### IV REGULATIONS FOR MATERNITY HOSPITALS OR SERVICES

All hospitals with maternity service as defined on page 1 of these regulations shall conform to the following standards in addition to those specified in the general regulations.

It will be noted that the regulations for maternity hospitals are more detailed and the standards are higher than those applying to other types of hospital service. This is because of the vital role of proper care in the reduction of maternal and infant mortality. Much attention has been given in recent years to efforts to reduce maternal and infant mortality through placing the pregnant woman under medical care early in pregnancy, educating her in the hygiene of pregnancy and the puerperium and stressing the importance of hospital delivery. Unless maternity hospital standards are kept at a reasonable level, this effort cannot be wholly effective. These regulations are intended not to hamper the physician with unnecessary red tape nor to dictate to him how he shall conduct his obstetrical work and keep his records but to aid him by pointing out what are regarded by leading obstetricians and hospital administrators as the essentials of good hospital delivery service and care of the newborn.

#### A. *Maternity units*

- 1 The maternity unit shall be segregated from any medical or surgical service. This shall not preclude the treatment of uninfected medical or surgical cases in separate rooms on a maternity unit.
- 2 There shall be at least one delivery room and hospitals with multiple bedrooms or wards shall provide in addition one or more labor rooms.
- 3 Isolation quarters shall be provided for infected mothers. A mother shall be considered infected if
  - a She has a communicable disease or is suspected of such or if she is a carrier.
  - b She nurses an infected infant.
  - c She is delivered outside the maternity unit of the hospital in which she is afterward cared for.
  - d She has an unexplained fever during the puerperium.

4. Labor, delivery room and all other facilities used for infected mothers shall be separate from, and not used for, non-infected patients until they are made safe by cleansing and sterilization.
  5. Equipment of a maternity unit shall include a bed-pan sterilizer or individual pans which shall be adequately sterilized for each patient.
  6. All nurseries, isolation quarters, formula rooms, examining rooms, labor and delivery rooms, and maternity rooms or wards shall have adequate facilities for the scrubbing of hands, and receptacles for the efficient temporary disposal of soiled linens and waste.
  7. Delivery-room technic must be in accordance with recognized and approved obstetrical technic. Equipment shall be such as to make this possible. Oxygen for resuscitation and facilities for blood transfusion shall be available.
  8. The advice of an obstetrical consultant should be obtained preceding any major operation or abnormal, induced or complicated labor.
  9. Before the removal of the mother or baby from the delivery room each infant shall be labeled with some adequate method of identification approved by the department.
  10. The 1 per cent solution of nitrate of silver furnished by the Department of Public Health shall be instilled in each eye of every infant before it leaves the delivery room.
  11. Should one or both eyes of an infant become inflamed, swollen and red, or show a discharge, the hospital shall report the case to the local board of health.
  12. When such a case is discharged from the hospital, a report in writing shall be sent within six hours after such discharge to the board of health of the city or town to which the infant is to be taken. This report shall state whether the infant is discharged cured or uncured, also the street and number to which the infant is to be taken.
  13. Each hospital shall act in conformity with the provisions of Chapter 119, General Laws (Tercenary Edition), as amended by Chapter 629, Acts of 1941, for the protection of children, and shall not be concerned in, encourage or permit any unlawful disposition of an infant or any arrangement whereby an infant may be deprived of any of his legal rights or be abandoned. The hospital shall not be concerned in placing infants apart from parents or guardian, and if the superintendent knows of any such arrangement he shall at once report the case to the Division of Child Guardianship of the Department of Public Welfare.
  14. Upon the discharge of each infant from the hospital, a mark specified by the department, which will serve to identify the infant, shall be placed upon the shirt, diaper, band, dress and other covering.
  15. Any neglect or evasion of these rules, or any collusion by the hospital with any person for their evasion, shall constitute sufficient cause for the revocation of the license.
- B. *Newborn nurseries.*
1. There shall be a separate nursery for newborn infants, with adequate space, light and ventilation.
  2. Bassinets shall be so spaced that they are separated by at least 6 inches on all sides. Suspension of bassinets on double-tier racks shall be prohibited.
  3. Isolation quarters shall be provided for infected infants. An infant shall be considered infected if:
    - a. It has a communicable disease or is suspected of such, or is a carrier.
    - b. If delivered of an infected mother.
    - c. If delivered outside the hospital.
  4. Common or group carriers for infants shall be prohibited.
  5. Cloth or paper covers on a common dressing table or scales shall be changed for each infant.
  6. Running hot and cold water and suitable receptacles for the disposal of waste and soiled linens shall be provided in or adjacent to each nursery.
  7. Individual sterilized rectal thermometers shall be provided for each infant. All examining instruments should be sterilized before use for each infant. Gauze, cotton and so forth shall be sterilized and kept stored in sterile containers in each nursery.
  8. All linens used in the nursery shall be kept separate from those used in other parts of the hospital and shall be laundered separately.
  9. All physicians and nurses and any others who must enter any part of the nursery shall scrub their hands thoroughly and put on a clean gown, headgear and mask.
- C. *Premature nurseries.* All hospitals with maternity service must provide the minimum equipment listed in this section for the care of premature infants. All standards specified in the section on newborn nurseries must be met in the premature nurseries; in addition, the following provisions shall be made:
1. The premature infant must be cared for in a heated bed or incubator, which must be available in all nurseries.\* (In a room with temperature and humidity control designed for the care of premature infants the heated bed is not required.)
  2. Some type of heated bed should be ready in the delivery room, in which the infant can be transported to the nursery.
  3. Oxygen must be quickly and easily available in both the delivery room and the premature nursery.
  4. Suction apparatus should be easily and quickly available in both the delivery room and the premature nursery.
  5. The premature should be cared for in a separate premature nursery or should be segregated in the newborn nursery.
  6. Isolation facilities must be provided for the infected premature infant.
  7. Nurses assigned to the care of premature infants shall not care for infected infants at the same time. Each nurse shall wash her hands for five minutes and put on a clean gown and mask before entering the premature nursery.
  8. Visitors must not be allowed in the premature nursery.
  9. The premature infant must not be discharged until it weighs more than 5 pounds and its condition is such that it will presumably survive home care.

\*A satisfactory incubator can be constructed for approximately \$10.00.

- 10 Before discharge, arrangements for continuous medical supervision by a physician or well child conference shall be reported by the staff physician to the superintendent

**D Formula rooms** Each maternity hospital shall have adequate facilities for the preparation of formulas for infants—where practical in a separate room. Proper sterilization and refrigeration equipment shall be provided in the formula room or in an adjoining room. Aseptic technic must be maintained in use of containers and utensils and in formula preparation

**E. Personnel in maternity units and nurseries**

**1 Nursing staff**

- Sufficient nurses shall be provided for the adequate care of mothers and infants. These shall be under the supervision, both night and day of a graduate nurse. After July 1, 1942, all new supervisors shall be graduates of an approved school of nursing and registered in Massachusetts.
  - Nurses assigned to nursery and formula rooms shall not come in contact with any infected patient or with isolation quarters.
  - Private nurses must comply with maternity unit rules and regulations.
  - No person shall enter the nursery except those immediately concerned with the care of the newborn.
- 2 All personnel in contact with patients and all food handlers shall be examined on assignment and annually thereafter by a physician designated by the hospital management and shall be certified as showing no evidence of communicable disease. This examination shall include a chest roentgenogram.
- 3 All personnel shall immediately report any illness, or signs of infection, however slight, and shall be excluded from the maternity unit until seen by a physician.

**F Visitors and visiting hours**

- Visiting hours to maternity services shall be set at such a time as not to coincide with the hours when the newborn infants are in the maternity ward or private rooms for nursing by their mothers. There shall be a minimum of visiting permitted on all maternity services.
- Children under fourteen years of age shall be prohibited from admittance to any maternity unit at any time.

**G Records** Complete and detailed case history records shall be kept of maternity patients and infants. The following outline gives the minimum information which should be included in any hospital maternity record. It is not of itself a record form.

**1 Maternal record**

Patients name, occupation, age, color, nativity, religion, gravida, address, husband's name and occupation, date of admission and service to which admitted, general history (medical, surgical, Wassermann tests), general physical examination on admission, obstetrical history of each pregnancy, describing prenatal care, month started and regularity, and all abnormalities.

Obstetrical examination on entrance to service including temperature, pulse, respirations, blood pressure, urinalysis (albumin and sugar), fetal heart rate and abnormalities.

Labor a satisfactory description of labor should be recorded, including time of onset, and if induced reasons therefor, maternal pulse rate during all stages, fetal heart rate. All rectal and vaginal examinations made in any stage of labor must be recorded as to time and findings, and by whom made. Analgesia or anesthesia and medication in any stage should be recorded as to type, amount and time given. In addition for each stage the following should be recorded:

First stage duration, type and frequency and character of pains, rupture of membranes, time whether spontaneous or artificial examinations, and anesthesia or analgesia as outlined in above paragraph, fetal heart rate.

Second stage duration, examination and anesthesia or analgesia described as outlined above, fetal heart rate, presentation, method of delivery—if operative reasons, descriptions and names of consultants and operator must be given, description of lacerations, description of any complications.

Third stage duration, method of placental delivery, hemorrhage, condition of uterus of mother and infant one hour after delivery. Name of physician who did delivery and assistants.

Postpartum course: chart of temperature every four hours when awake for five days, then twice daily, if any complication arises, resume four hour chart; medication and treatment, progress of involution of uterus, type of lochia, condition of breasts and nipples, general condition of mother (including condition of uterus) at time of discharge, date of discharge.

**2 Pediatric record**

Infant's name, sex, color, date and hour born, birth weight and length, period of gestation, mother's name, address.

Description of complications of pregnancy or delivery, condition at birth, including color, quality of cry, method and duration of resuscitation.

Findings of initial general physical examination, description of any postnatal disturbances.

Progress notes, chart of temperature, pulse and respirations at least twice a day if no complications arise, weight chart recording weight at least every other day, condition of cord from day to day, color from day to day, feeding character and frequency of stools, vomiting, any unusual symptoms.

Findings of physical examination on discharge with recommendations.

Physician's name.

**V REGULATIONS FOR TUBERCULOSIS SANATORIUMS**

All provisions of the general regulations shall apply to tuberculous hospitals and sanatoriums. In addition, the following special requirements must be fulfilled:

**A Equipment**

- 1 Each hospital, irrespective of its size, shall have x-ray equipment capable of producing satisfactory

diagnostic roentgenograms of the chest and making fluoroscopic examinations of the chest.

2. There must be apparatus for the administration of artificial pneumothorax.

#### B. Procedures.

1. Each patient shall have a medical history taken and physical examination made by a physician within four days of admission.
2. All patients with expectoration shall have their sputum examined for tubercle bacilli by direct smear on admission, and if the smears are negative, more sensitive methods for the detection of tubercle bacilli (concentration tests, cultures or guinea pig inoculation) must be employed. Sanatoriums with less than 50 beds may arrange to have a laboratory, approved by the department, perform these tests. All patients who are raising sputum, with the exception of progressive far-advanced cases, should have their sputums examined at least once a month.
3. All patients shall have a chest roentgenogram on admission and as often thereafter as is necessary to detect changes in the pulmonary lesions, with a maximum interval of once in four months, and within two months of discharge.
4. Patients shall be provided with cardboard sputum boxes and paper handkerchiefs or satisfactory substitutes therefor, which shall be destroyed by incineration after use. Reasonable precautions shall be taken against exposing personnel and other patients to infection from sputum-positive cases.

#### C. Personnel.

1. Each hospital shall have either on its resident or visiting staff at least one properly qualified tuberculosis specialist.
2. Whenever indications exist, examination and treatment by a consulting nose and throat specialist shall be provided. Arrangements shall be made for the performance of bronchoscopy whenever, in the opinion of the staff, this procedure is indicated.
3. The services of a dentist shall be provided regularly and as needed.
4. All personnel regularly employed in the hospital who come in contact with patients shall have a roentgenogram of the chest at least annually.

## BOOK REVIEWS

*Essentials of Endocrinology.* By Arthur Grollman, Ph.D., M.D. 8°, cloth, 480 pp., with 74 illustrations. Philadelphia: J. B. Lippincott Company, 1941. \$6.00.

This book is intended as a broad survey of the entire subject of endocrinology for the "average medical reader," and serves as a good up-to-date summary of this rapidly developing field.

The author is primarily a pharmacologist and has been a chemist and physiologist. It is not surprising, therefore, that his approach is that of the laboratory experimenter rather than that of the clinician.

After an introductory chapter, the author takes up each endocrine gland in turn, grouping together the glands of the cranial cavity, the branchiogenic organs, the abdominal endocrines, the hormones of the reproductive system and the hormones derived from nonendocrine organs. In discussing each gland, he gives a rather detailed account of its embryology and histology, and draws heavily on the available data from comparative anatomy. The physiology and the principal experimentally proved facts are concisely presented, whereas all theories and ideas not conclusively proved experimentally are given short shrift.

Many widely held notions are dismissed as without valid foundation. Thus, the conception of the pituitary gland as secreting numerous separate hormones "is undoubtedly erroneous, and future investigation may reveal that the hypophysis elaborates a single hormone which is responsible for all of the manifestations of the gland."

The clinical aspects of endocrinology, including therapy with the available preparations, are by no means neglected; yet they are given relatively less consideration than the "average medical reader" might wish. There are a few statements that might be questioned. For example, in the treatment of myxedema, the author states that it is "safe to initiate therapy with a daily dose of 2 grains [of thyroid]." In discussing the causes of destruction of the anterior portion of the pituitary gland in Simmonds's disease, he states that "the most common one is emboli originating usually in the parturient uterus which occlude the terminal arteries of the anterior hypophysis."

On the whole, this is a well-written, critical textbook. There are well-chosen references at the end of each chapter, a good index, and a table, in the front and back linings, of some commercially available endocrine products and their standardization. Unfortunately, there are numerous typographical errors.

*The Biologic Fundamentals of Radiation Therapy.* A textbook. By Friedrich Ellinger, M.D. With a preface by Maurice Lenz, M.D. English translation by Reuben Gross, M.D. 8°, cloth, 360 pp., with 79 illustrations. New York: Elsevier Publishing Company, Incorporated, 1941. \$5.00.

The book covers more ground than its title implies. In addition to the biologic fundamentals, it also delves into the underlying principles of electrophysics that pertain to this subject. Although the part of the light spectrum that is therapeutically most important will remain invisible to the *physical* eye of the reader, this book will enable him to see it with his *mind's* eye.

The introduction describes the electromagnetic spectrum and the combination of the quantum and wave theories of light. A section on biologic considerations or the action of radiation on living matter follows. This leads to discussions of absorption of radiation by the respective medium and of the effective quantum energy as a function of wave length at the site of absorption. In the light of these and similar basic principles, roentgen-rays, the gamma radiation of radium, the Grenz rays (ultrasoft roentgen rays), ultraviolet rays and the action of visible light are successively treated.

The technic of application of these energies to the various tissues, organs and systems of the body is discussed in the light of the previously mentioned physical principles and biologic effects.

Important factors, beneficial and injurious, that are manifested by the local reaction of the skin, the portal of entry of these rays, and their indirect effects on the deep-seated structures of the body are taken up in a logical and scientific manner.

The author is as honest in his statements of fact and hypothesis as he is profound in his discussion of the underlying theory. He is as generous in the details of technic of application as he is broad in his consideration of the various physiologic and pathological problems that confront the physician in his practice of medicine. The reviewer therefore heartily endorses this work to the student, general practitioner and specialist alike. Radiation therapy, particularly that employing the ultraviolet ray, has been used widely but not always wisely. This treatise may help to remedy the situation.

(Notices on page x)

# The New England Journal of Medicine

Copyright, 1942 by the Massachusetts Medical Society

VOLUME 226

JUNE 25, 1942

NUMBER 26

## THE TREATMENT OF PERNICIOUS ANEMIA: A NINE-YEAR STUDY OF MAINTENANCE REQUIREMENTS, WITH A NOTE ON THE EFFICACY OF PURIFIED LIVER EXTRACTS IN THE CONTROL OF NEURAL LESIONS\*

MAURICE B. STRAUSS, M.D.,† ARTHUR J. PATEK, JR., M.D.,‡ FREDERICK J. POHLE, M.D.,‡ HERBERT J. FOX, M.D.,§ AND JOSEPH H. BUCHENAU, M.D. |

BOSTON

IT has been well established that the patient with Addisonian pernicious anemia may be maintained in complete remission with "adequate" liver extract administered parenterally. Furthermore, it is well known that such treatment must be continued throughout the remainder of the patient's life. What constitutes "adequate" therapy, however, is not well established. Although probably over 90 per cent of patients with pernicious anemia may be maintained satisfactorily if they receive a minimum of 1 U.S.P. unit of liver extract daily, generally administered as 15 units every fortnight or 30 units monthly, there is a question whether this amount is in excess of the requirements of most patients. Intervals longer than one month between injections are considered inadvisable for most patients, since it has been shown that relapse may occur as soon as eight to twelve weeks after the injection of even massive doses of liver extract.<sup>1,2</sup> Whether benefit derives from shorter intervals than one month between injections is not known.

In an endeavor to clarify these problems, an analysis has been made of the blood levels of 80 patients with pernicious anemia who received liver extract in varying amounts and at varying intervals during a period extending from five to nine years. The minimum length of any one mode of treatment was one year, and no patient has been in-

cluded in this study who was not treated for at least five years. During the first part of this study, the liver extract originally described by Strauss, Taylor and Castle<sup>3</sup> was employed in uniform dosage of 10 cc. per injection,<sup>4</sup> at intervals of one to four weeks. The average red-

TABLE 1 Effect of Varying the Time Interval between Injections of Liver Extract

No. of Patients	Percent of Liver Extract Given at Each Injection	Interval between Injections	Average Capillary Hemoglobin	Average Capillary Hemoglobin
	cc.	Weeks	gms.	gms.
24	10	1	4.8	92
	15	2	4.8	92
15	15	1	4.8	92
	15	2	4.9	93
14	15	1	4.7	92
	15	2	4.7	94
45	10	2	4.7	93
	10	3	4.5	95
47	15	2	4.7	93
	15	4	4.3	93
41	15	3	4.5	95
	15	4	4.5	93

cell counts for patients receiving injections at intervals of one, two, three and four weeks were 4,780,000, 4,720,000, 4,850,000 and 4,750,000, and the hemoglobin levels were 91, 92, 94 and 91 per cent respectively (100 per cent being equivalent to 15.6 gm. per 100 cc.). To facilitate comparison, the patients were divided into six groups, each group consisting of patients who received injections at different intervals (Table 1). It is apparent that varying the interval between injections

\*From the Thayer Memorial Laboratory, Boston City Hospital, and the Department of Medicine, Harvard Medical School.

†Associate in medicine, Harvard Medical School, assistant physician, Thayer Memorial Laboratory, and the Department of Medicine, Boston City Hospital.

‡Formerly assistant in medicine, Harvard Medical School, and assistant physician, Thayer Memorial Laboratory, Boston City Hospital.

§Formerly, assistant in medicine, Harvard Medical School, and assistant resident physician, Thayer Memorial Laboratory, Boston City Hospital.

|Formerly, fellow in medicine, Harvard Medical School, assistant resident physician, Thayer Memorial Laboratory, Boston City Hospital.

The authors are indebted to Dr. J. C. Castle for his critical review of the manuscript, and to Dr. J. C. Castle for his critical review of the manuscript.



from one to four weeks was without effect on either the red-cell count or the hemoglobin level.

In 1938, three changes were made: a uniform interval of four weeks between injections was adopted for all patients; a shift was made from the relatively dilute type of liver extract previously employed to Solution Liver Extract Purified, Lilly, containing 15 U.S.P. units to each cubic centimeter; and blood for examination, formerly obtained by puncture of the ear lobe, was removed by venipuncture without stasis. It has been pointed out that, in pernicious anemia at least, venous blood contains approximately 5 per cent less hemoglobin and 250,000 fewer erythrocytes per cubic millimeter than capillary blood.<sup>4</sup> The amount of extract given at each injection was 10, 15, 20 or 30 units. The average red-cell counts maintained with each of these doses were 4,540,000, 4,470,000, 4,470,000 and 4,520,000, and the hemoglobin levels were 85, 87, 87 and 88 per cent respectively. At the end of 1939, the amount of extract received by 45 of the patients was increased by 50 per cent. Table 2 shows the ab-

complained of feeling less well during the third or fourth week after the injection, and during the period immediately preceding the next injection, and a few actually had some subjective manifestations of glossitis that were abolished after the injection.

Since this study was completed, we have adopted a uniform maintenance dose of 15 U.S.P. units of purified liver extract every four weeks for all clinic patients. In the period of eighteen months in which this regimen has been in effect, we have encountered no relapses in the blood, gastrointestinal or nervous systems, either objective or subjective.

### DISCUSSION

There seems to be little doubt that individual maintenance requirements for liver extract vary widely in patients with Addisonian pernicious anemia. The determination of the requirement is a difficult task often necessitating years of observation. It is not, in general, a feasible procedure in the routine handling of a patient with pernicious anemia. It has repeatedly been stated that one of the criteria of adequate treatment is the maintenance of normal red-cell values. This is, of course, quite correct, although often difficult to apply in actual practice for several reasons. One of these is that although the *average normal* red-cell count is in the neighborhood of 4,500,000 to 5,000,000, there are rare persons whose *normal* values are persistently under 4,000,000 and others whose normal values are over 6,000,000. A second difficulty, only recently appreciated,<sup>7</sup> is the fact that a single red-cell count performed with satisfactory technic in the usual manner at an approximate level of 5,000,000 is significant only within a range of 1,600,000. In fact, a difference of over 1,000,000 may be expected to occur once in every twenty pairs of consecutive red-cell counts. The performance of duplicate determinations on each observation only increases the range of significance to 1,100,000 and quadruplicate counts to 800,000. A mean of twenty counts is significant within a range of 340,000, but this is hardly a practical procedure. Price-Jones curves, admittedly the most accurate determination of red-cell normality, are too laborious for routine use. Estimation of the mean corpuscular volume, depending as it does on the red-cell count and hematocrit determination, appears to be subject to even wider variation than the red-cell count alone.

In view of these difficulties, we have set up the following procedure in our clinic for determining adequacy of treatment:

If the red-cell count is persistently under 4,000,000, greatly augmented doses of liver extract are employed at short intervals — such as 30 to

TABLE 2. *Effect of Increasing the Amount of Liver Extract Given at Each Injection.*

NO. OF PATIENTS	AMOUNT OF LIVER EXTRACT GIVEN AT EACH INJECTION	INTERVAL BETWEEN INJECTIONS	AVERAGE VENOUS RED-CELL COUNT	AVERAGE VENOUS HEMO- GLOBIN
	U S P. units	weeks	$\times 10^6$	%
25	10	4	4.5	85
	15	4	4.5	87
20	20	4	4.5	87
	30	4	4.5	88

sence of effect of this procedure on the red-cell count and hemoglobin level.

In the first part of these observations, no case of blood relapse occurred with the increased interval between injections, and in the second part there was no statistically significant improvement in any patient's blood values with the 50 per cent increase in dose.

Additional evidence of the adequacy of the treatment employed is to be found in the facts that no patient with subacute combined degeneration of the spinal cord suffered a neural relapse and that no patient without spinal-cord manifestations developed neural lesions during the period of observation.<sup>5</sup>

It may also be stated that the concentrated liver extract employed during the last three years has been as effective in controlling the neural lesions as the less purified extracts previously used.<sup>6</sup>

When injections of 10 cc. of crude extract or 10 U.S.P. units of purified extract were given at intervals of three or four weeks, certain patients

75 U.S.P. units weekly for two or three months; if this results in consistently higher blood values, one concludes that the previous therapy was inadequate.

If glossitis occurs, the treatment is considered inadequate, irrespective of high red-cell levels.

If neural lesions progress unfavorably, the treatment is considered inadequate, irrespective of red-cell counts.

If the patient lacks what he considers a satisfactory sense of well-being on any given amount of treatment and regains a feeling of better health when, unknown to him, he is receiving a larger amount of extract, the original treatment is regarded as inadequate.

### SUMMARY

Eighty patients with Addisonian pernicious anemia were studied for from five to nine years while under treatment with liver extract parenterally administered.

In these 80 patients, no difference in blood levels was detected when the time interval between injections of the same amount of dilute liver extract varied from one to four weeks. Seventy-five patients subsequently received concentrated liver

extract by injection. No difference in blood levels was noted as a result of this change, and there was no case of neural relapse.

No difference in blood levels between patients receiving a minimum of 10 U.S.P. units every four weeks and those receiving larger amounts was detected. It is nevertheless probable that certain patients require more liver extract than this amount, particularly in the presence of infection or severe damage to vital organs.

### REFERENCES

1. Strauss M B and Pollok F J. The duration of remission in pernicious anemia with liver therapy: the efficacy of massive doses administered at one time. *J A M A* 114 1318 1320 1940
2. Seymour W B, Heimle R W and Miller F R. Liver dosage in pernicious anemia: failure of quantitative storage of hematopoietic principle. *New Eng J Med* 225 675 679 1941
3. Strauss M B, Taylor F H L, and Castle W B. Intramuscular use of liver extract: maximal responses of reticulocytes from daily intramuscular injection of extract derived from ten grams of liver [preliminary communication]. *J A M A* 97 313 1931
4. Strauss M B and Burchenal J H. A comparison of capillary and venous red blood cell counts and hemoglobin determinations in patients with pernicious anemia in remission under treatment. *J Lab & Clin Med* 27 137 1942
5. Strauss M B, Solomon P and Fox H J. Combined degeneration of the spinal cord in pernicious anemia: the results of seven years' experience with parenteral liver therapy. *New Eng J Med* 222 373 375 1940
6. Strauss M B. Unpublished data.
7. Berkson J, Majath T B and Hurst M. The error of estimate of the blood cell count as made with the hemocytometer. *Am J Physiol* 128 309 373 1940

## PNEUMOCOCCAL MENINGITIS\*

### A Study of Seventy-Two Cases

HARRY F. DOWLING, M.D.,† CARL C. DAUER, M.D.,‡ HARRY A. FELDMAN, M.D.,§ AND CLARENCE R. HARTMAN, M.D.¶

WASHINGTON, D. C.

BEFORE the use of the modern specific therapeutic agents, pneumococcal meningitis was almost invariably fatal. With the advent of specific serum and particularly since sulfanilamide and its derivatives have become available, a number of cases have been reported in which a relatively large proportion of patients recovered. Steele and Gottlieb,<sup>1</sup> reviewing the 115 sulfonamide-treated cases reported in the literature through June, 1940, found that recovery occurred in 60 per cent. Since June, 1940, two equally favorable reports have appeared. Rhoads and his associates<sup>2</sup> reported a recovery rate of 32 per cent among 22 patients treated with sulfapy-

ridine and specific serum; Neal and her co-workers<sup>3</sup> presented a series of 30 patients treated with sulfapyridine, of whom 10 (33 per cent) recovered.

To determine exactly how the recovery rate from this disease has been influenced by the newer therapeutic agents, we have studied all the cases of pneumococcal meningitis occurring in the District of Columbia from January 1, 1938, to October 31, 1941. It was hoped that by this method all selection of cases would be eliminated and a true picture of the mortality rate and the factors governing it could be obtained. Data on 72 cases of meningitis identified as caused by the pneumococcus were obtained from hospital and health-department records. This group includes all the cases recognized in the District of Columbia during the period mentioned. The occurrence of the cases by years is shown in Table 1. Fifty-one, or 71 per cent of all the cases, occurred during the late fall and winter months, November to 1, inclusive. This seasonal distribution is

\*From the Health Department, District of Columbia, and the Department of Medicine, George Washington University School of Medicine.

†Clinical professor of medicine, George Washington University School of Medicine; chief, George Washington Medical Division, Gallinger Municipal Hospital.

‡Epidemiologist, Health Department, District of Columbia; clinical instructor in medicine, George Washington University School of Medicine.

§Formerly, fellow in medicine, George Washington University School of Medicine.

¶Formerly, clinical instructor in medicine, George Washington University School of Medicine.

quite similar to that of pneumococcal pneumonia. The age, sex and race of the 72 patients are shown in Table 2. The largest percentage of cases occurred in children under one year of age (31 per cent) and the next largest in adults over the age of sixty years (15 per cent). Three of the 4 patients who recovered were young adults (twenty-four, twenty-eight and thirty years of age),

TABLE 1. Occurrence of Cases of Pneumococcal Meningitis by Years in the District of Columbia.

YEAR	NO. OF CASES	NO. OF RECOVERIES	FATALITY %
1938	18	0	100
1939	16	2	88
1940	19	1	95
1941 (10 months)	19	1	95
Totals	72	4	
Average			94

and the fourth was an infant three months old. The ratio of male to female cases was 1.6:1.0.

The pneumococci most frequently encountered (Table 3) were Types 3 (14 cases), 5 (6 cases) and

TABLE 2. Age, Sex and Race in Cases of Pneumococcal Meningitis.

AGE	MALE		FEMALE		TOTAL NO. OF CASES	TOTAL NO. OF RECOVERIES
	WHITE	COL-OR'D	WHITE	COL-OR'D		
yr.						
Under 1	6	6	3	7	22	1*
1-10	5	1	1	3	10	0
11-20	0	1	1	0	2	0
21-30	3	2	0	2	7	3*
31-40	0	1	0	1	2	0
41-50	4	3	2	0	9	0
51-60	5	0	2	2	9	0
61 and over	6	1	2	2	11	0
Totals	29	15	11	17	72	4

\*All colored patients.

14 (6 cases). Two of the first type were found in patients under two years of age, and the remaining patients were fifteen years or older. Both cases of Type 6, which is commonly encountered in children, occurred in children under two years of age. Type 16, another type found in children, was recovered from 3 infants under one year and from 3 adults. The type of pneumococcus was not determined in 9 of the 72 cases. As shown in Table 4, a history of middle-ear infection and pneumonia during or immediately preceding the development of meningitis was found in a large proportion (58 per cent) of the cases. A history of milder respiratory infections was found in an additional 21 per cent. The occurrence of otitis media was found as frequently among adults as among children. Sixty-seven of the 72 patients received one or more of the sulfonamide drugs or specific serum,

or both. In 5 cases, the meningitis appeared to develop while active treatment for pneumonia with a sulfonamide was in progress. Five patients received no serum or chemotherapy either because they died before treatment could be started or because the meningitis was not immediately recognized.

To determine whether or not therapy was adequate in each of the 67 cases, the treatment was classified as "good," "fair" or "poor." "Good" treatment with one of the sulfonamides was considered to mean: that the initial dose was 4 to 6 gm., followed by 1 gm. every four hours, in adults,

TABLE 3. Types of Pneumococci Found on Examination of Spinal Fluid in Cases of Pneumococcal Meningitis.

TYPE	NO. OF CASES
1	1
2	3
3	14
4	4
5	6
6	2
7	4
8	4
10	3
12	4*
14	6*
16	1†
17	1
18	5
19	3
23	1
Carver	1†
Not typed	9
Total	72

\*One recovery.  
†Recovery.

with comparable doses for children; that the concentration of the drug in the blood and cerebro-spinal fluid was kept at high levels; and that no lapses in the drug therapy occurred from the time the meningitis was first treated until death or

TABLE 4. History of Infections and Injuries Preceding Onset of Pneumococcal Meningitis.

INFECTION OR INJURY	NO. OF CASES	PER CENT	NO. OF RECOVERIES
Otitis media, mastoiditis	21	29	1
Pneumonia	18	25	0
Pneumonia (questionable)	3	4	1
Otitis media and pneumonia	2	3	0
Other respiratory infections*	15	21	0
Fracture of skull	3	4	0
None	10	14	2
Totals	72		4

\*Includes common cold, influenza and sinusitis.

recovery ensued. "Good" treatment with specific serum was considered to mean the administration of large doses of serum by the intravenous route, with or without additional serum intrathecally and intramuscularly, begun as soon as the meningitis was recognized and repeated at frequent intervals as long as the condition of the patient

required it. The treatment in cases not meeting the above standards completely was classified as 'fair,' and that in cases in which these conditions were fulfilled only slightly was considered 'poor.'

As indicated in Table 5, 39, or 54 per cent, of the patients received what might be regarded as good treatment, 19, or 26 per cent, had fair treatment, and 9, or 13 per cent, were poorly treated. Of the 17 patients who received good treatment with

Gottlieb can easily be determined from a study of their article. Thirty of the cases in their review were published as individual case reports, and among these, 27 patients recovered. Furthermore, among the 18 cases reported in groups of two or three, there were 12 recoveries. From these figures, it is obvious that cures from this disease have heretofore been so infrequent as to lead authors to publish isolated recovered cases, whereas the

TABLE 5 *Quality of Treatment Administered and Its Results in Cases of Pneumococcal Meningitis*

QUALITY OF TREATMENT	SERUM ALONE		DRUG ALONE		SERUM AND DRUG		TOTAL		AVERAGE SURVIVAL IN FATAL CASES
	NO. OF CASES	NO. OF RECOVERIES	NO. OF CASES	NO. OF RECOVERIES	NO. OF CASES	NO. OF RECOVERIES	NO. OF CASES	NO. OF RECOVERIES	
Good	0		1	1	2	3	9	4	7.5
Fair	0		14	0	5	0	19	0	2.6
Poor	3	0	3	0	3	0	9	0	7.1
None							5	0	1.2

drugs alone, 5 received sulfanilamide, 9 had sulfapyridine (1 of whom recovered) and 3 had both drugs. Of those receiving good treatment with drugs and serum, 2 had sulfanilamide and serum, 14 had sulfapyridine and serum (2 of whom recovered), 3 had sulfanilamide, sulfapyridine and serum (1 of whom recovered after receiving large doses of sulfapyridine by mouth together with a small dose of sulfanilamide subcutaneously), 3 had sulfathiazole with sodium sulfapyridine and serum, 1 had sulfadiazine and serum and 1 had sulfathiazole, sulfanilamide and serum. None of the patients survived who received treatment classified as fair or poor.

One effect of therapy that has been neglected in the study of infectious diseases having a high mortality rate is the survival in patients who eventually succumb to the disease. This aspect has been considered in the last column of Table 5. Patients who received good treatment lived for an average of 7.5 days from the time meningitis was diagnosed until death. This is a considerably longer period than the average survival of 2.6 days and 2.1 days for patients given fair and poor treatment. The patients receiving no specific treatment lived an average of 1.2 days after the recognition of the disease.

#### DISCUSSION

Steele and Gottlieb,<sup>1</sup> in their review of the literature through June, 1940, covering 115 cases of pneumococcal meningitis treated with the sulfonamides, found that 69, or 60 per cent, of the patients recovered. The general experience of those interested in this disease indicates that such a recovery rate is unusually optimistic. The reason why this high figure was obtained by Steele and

bulk of unsuccessfully treated cases remains unreported.

The recovery rate was somewhat lower (45 per cent) among the remaining cases in Steele and Gottlieb's review (reported in groups of four or more). In the two large series of cases reported since the above review was made, as previously mentioned, the recovery rates were still lower, Rhoads and his associates<sup>2</sup> reporting 32 per cent recoveries among 22 patients and Neal et al.<sup>3</sup> 33 per cent among 30 patients. Thus, it is seen that the larger the number of cases in a given series the lower the recovery rate. If a large enough series of cases were studied especially if all the cases occurring in a given area were included, a figure close to the true recovery rate would be obtained. This is what we have attempted to do in the present study, with the result that we have found only 4 recoveries among 72 patients. When the patients who did not receive adequate treatment are eliminated from the study, there remain 39 patients, among whom 4, or 10 per cent, recovered. This may be considered the percentage of recoveries obtained by physicians in this locality in private and hospital practice, using the optimum treatment available at the present time.

Fourteen of the patients in the present series were treated by us personally at the Gallinger Municipal Hospital, with 3 (21 per cent) recoveries. This recovery rate probably represents the usual percentage of recoveries achieved by an active medical service interested in infectious diseases and equipped with the facilities for rapid diagnosis and treatment of pneumococcal meningitis.

If 21 per cent, or approximately one fifth, of the patients with pneumococcal meningitis recover with the best treatment available at present, what

factors appear to alter the prognosis in the individual case? A study of our cases, together with a review of those reported in the literature that have been treated with the sulfonamides, makes it evident that patients who exhibit no other focus of infection are likeliest to get well. We have observed, as Rhoads and his associates have, that when there are many cells and few organisms in the cerebrospinal fluid, the prognosis is distinctly better than when there are fewer cells and many bacteria. A higher death rate occurs in the very young and the very old, as in most infectious diseases. The type of infecting pneumococcus seems to have no effect on the prognosis. We could find no correlation between the day on which treatment was begun and the outcome of the case. However, since the diagnosis was not always made promptly and since it was difficult to determine the exact onset of the disease in many cases, these data are not very reliable.

Our figures indicate that sulfapyridine is superior to sulfanilamide, since all 4 recoveries occurred among the 41 patients treated with sulfapyridine with and without serum, and none of the 30 patients treated with sulfanilamide, alone or with serum, recovered. The few patients treated with sulfathiazole and the 1 patient treated with sulfadiazine died. It is quite likely that Steele and Gottlieb's finding that a greater percentage of patients recovered after receiving sulfanilamide than after the administration of sulfapyridine was due to the fact that sulfanilamide was the first of the drugs to be used and any recovery was worth reporting. By the time sulfapyridine was introduced, recovery from pneumococcal meningitis was no longer rare, and many cases of recovery were undoubtedly not reported.

No conclusion can be drawn from our cases concerning the efficacy of specific serum in addition to the sulfonamides. Three of our patients who were children, occurring in 1 case of Type 1 and 2 cases of Type 2, were recovered and from 3 cases of Type 2 was not determined.

As shown in the preceding table, infection preceded treatment in 1 case. A higher percentage was found in a series of 100 cases. A higher percentage was found in a series of 100 cases.

Sixty-seven cases more of the

recovered received the combined therapy, whereas the fourth received sulfapyridine alone. Until more evidence is available, we believe that serum and sulfapyridine or sulfadiazine should be used in combination.

### SUMMARY

An analysis of all the cases of pneumococcal meningitis, 72 in number, occurring in the District of Columbia between January 1, 1938, and October 31, 1941, is presented.

Only 4 of these patients survived, all of whom were classified among the group of 39 patients who received good treatment with the sulfonamide drugs or specific serum or both. Among the 19 patients who were given only fair treatment, the 9 patients who received poor treatment and the 5 patients who received no specific treatment of any kind, there were no recoveries.

Among the fatal cases, those receiving good treatment survived an average of 7.5 days after the meningitis was diagnosed, and those who were given fair, poor or no treatment survived an average of 2.6, 2.1 and 1.2 days, respectively.

With the best treatment at our disposal today, on an active medical service interested in infectious diseases and equipped with facilities for rapid diagnosis and treatment, the mortality rate from pneumococcal meningitis is about 80 per cent.

The factors influencing the prognosis and treatment of pneumococcal meningitis are discussed.

### REFERENCES

1. Steele, C. W., and Gottlieb, J. Treatment of pneumococcal meningitis with sulfanilamide and sulfapyridine: a statistical study of all reported cases in which chemotherapy was used, with or without specific antipneumococcus serum. *Arch. Int. Med.* 68:211-231, 1941.
2. Rhoads, P. S., Hoyne, A. L., Levin, B., Horswell, R. G., Reals, W. H., and Fox, W. W. Treatment of pneumococcal meningitis. *J. A. M. A.* 115:917-922, 1940.
3. Neal, J. B., Applebaum, E., and Jackson, H. W. Sulfapyridine and its sodium salt in the treatment of meningitis due to the pneumococcus and haemophilus influenzae. *J. A. M. A.* 115:2055-2058, 1940.

THE RECLASSIFICATION OF REPORTED CASES OF  
TUBERCULOSIS IN MASSACHUSETTS

## Present Report

Edward J. Welch, M.D., and Peter Zuck, M.D.

242

SINCE 1917, pulmonary tuberculosis has been by law a reportable communicable disease in Massachusetts. All other forms of tuberculosis have, since that time, been added to the list of reportable diseases. With the intensification of the legal requirements, there came increased attention on the part of private physicians, local health agencies and the Massachusetts Department of Public Health in finding, treating and following these cases. Altogether, 209,892 cases have been reported in Massachusetts from 1917 to 1940. The percentage of the actual cases that this figure represents is not known. Although the majority of physicians have been conscientious in reporting their cases, others have been lax in this duty. Often, to satisfy a patient's desire for secrecy, reporting of the case has been omitted, the health authorities have had no opportunity to guide the patient, if treatment is neglected, and no search for contact cases has been made. Fortunately, as tuberculosis has come more into the open and as hopeful programs of prevention and treatment have developed, this type of neglect has diminished. Today, the chief sources of error by the physician in failing to report cases appear to be missed diagnoses and lapses of memory.

The duties of the practicing physician are few and simple to report each case on the proper form to the local board of health, to arrange for treatment and continued observation of the patient in competent hands, with public health supervision or hospitalization in a sanatorium for the case with positive sputum, and to arrange or to allow the public health nurse to arrange for the examination of contacts.

A more frequent resort to roentgenograms of the chest, to thorough sputum analysis for tubercle bacilli (including the more sensitive methods if smears are negative) and, finally, to consultation in suspected cases will prevent missed diagnoses in pulmonary cases. In extrapulmonary cases, which are usually recognized with less difficulty, doubt should also lead to consultation.

The duties of the local boards of health in reported cases are as follows: the physician in charge of the case should be consulted and a

been the main factor in the progress of the case as  
 given by the medical expert, and the patient  
 negligence in the matter of the doctor's visit to the  
 hospital and the doctor's treatment, and the  
 patient's failure to take proper treatment and to  
 have regular checkups by his physician or im-  
 proper treatment by his doctor should be investigated  
 and a report should be made to the examining  
 committee and the committee of the physician in  
 which the above are need for this.

In 1938, the Division of Tuberculosis of the Massachusetts Department of Public Health first undertook to investigate and advise local boards of health regarding their lists of reported cases. It was found that in most localities these lists had grown to such a high figure that it was beyond the ability of the local nurse to follow every case. Many lists had not even been corrected for deaths, removals to other towns, unlocated cases and so forth. It was believed that it would be possible to revise these lists by a reclassification of all reported cases and by the establishment of new lists for the cases still in need of observation. This revision was first carried out during the summer months when the personnel of the state school clinics was available to do the work. Since July 1939, the work has been carried on throughout the year aided by a grant from the United States Public Health Service providing for full time personnel and necessary equipment. It has been possible, as a result of this study, to reduce the lists of cases requiring further observation to a workable number. It is hoped that this will stimulate greater activity by the boards of health in following tuberculous patients and their families.

The reclassification has been carried out thus far in one hundred and thirty cities and towns of Massachusetts, in most of which clinics have been held following a preliminary exclusion of all deaths removals to other places and unlocated cases. Cases having recent roentgenograms of the chest—that is within twelve months—available in local sanatoriums were first reviewed there and if possible, were reclassified without being invited to the clinic. A home visit was made in each of the remaining cases by the local public health nurse, and the patient was asked to attend the clinic. Of those refusing to come either local

Assistant in Medicine Boston University School of Medicine  
 Physician in Chief Channing Home Boston  
 Chief of Clinics Division of Tuberculosis Massachusetts Department  
 of Public Health

histories or x-ray films were reviewed, and the cases thus reclassified.

As the patients come to the clinic, complete medical histories of their disease are recorded, and physical, x-ray and sputum examinations made. The cases were finally classified as follows.

*Active list.* This group, which requires further study, includes all pulmonary cases showing active disease by clinical findings, by x-ray examination or by positive sputum; all cases in sanatoriums at the time of reclassification; cases thought to be inactive clinically but not yet followed long enough to be unmistakably so; all cases under collapse therapy (including thoracoplasty cases), regardless of health or x-ray findings; and extrapulmonary patients in sanatoriums who have discharges or clinically active disease.

*Inactive list.* This group, which does not require further follow-up, comprises inactive

own merits. It is impossible to establish fixed rules for such a procedure. Ideally, every case of pulmonary tuberculosis would be followed by periodic checkup into old age. With the scant funds and limited personnel usually assigned to tuberculosis work in most communities, such a program is impossible, and the number of cases to be followed must be kept at a workable figure. Although it is apparent that almost any case of pulmonary tuberculosis may become reactivated, cases with a long history of arrested disease are less apt to do so than those known to have had recent activity. Arbitrarily, then, in a reclassification of this sort, the latter group constitutes the bulk of cases kept for observation after an initial list of cases with active disease has been established. Emphasis falls, of course, on the pulmonary group, in which the real menace to the public health lurks. In all cities and towns where we have conducted clinics, we have attempted to

TABLE 1. *Summary of Findings in 2286 Reclassified Cases.*

TYPE OF CASE	No. of CASES	CLASSIFICATION			
		ACTIVE LIST	INACTIVE LIST	CONTACT OBSERVATION	SCHOOL CLINIC
Cases at sanatoriums	277	277	0	0	0
Cases with local x-ray films reviewed	842	554 (65%)	264	18	6
Refusals					
X-ray films reviewed	54	22 (40%)	29	3	0
Histories reviewed	397	199 (50%)	192	4	2
Cases examined and x-rayed	716	159 (22%)	528	19	10
Totals	2286	1211 (53%)	1013	44	18

cases of pulmonary tuberculosis in which the patient has been symptom free for several years and in which there is x-ray evidence of healed fibrotic or calcified lesions, or negative x-ray films and negative sputum—in many cases, films taken over a period of eight to ten years are available for determination of the status of the lesions; pulmonary cases proved to be non-tuberculous, including bronchiectasis, asthma and cardiac disease; extrapulmonary cases without symptoms, physical signs or discharges, and having a negative x-ray film of the chest; and childhood-type cases in patients past school age.

*Contact observation.* This group includes reported cases without present evidence of tuberculosis but kept for observation because of contact history.

*School clinic.* This group consisted of primary (childhood-type) cases of school age, kept for observation by the school clinic. (It should be noted that primary tuberculosis is no longer a reportable disease in Massachusetts.)

The reclassification of the individual case is a difficult problem, each case being decided on its

emphasize the value of control of proved cases. The follow-up of negative contacts (especially in children under ten years of age) is overdone in many communities, is of secondary importance and should be sacrificed when economy of effort is required.

At the end of the reclassification in each city or town, every patient who comes to the clinic is sent a letter stating the reclassification. Patients whose names are placed on the inactive list are advised to have an annual physical examination by their own physicians and to seek advice and treatment at once if they should ever have a return of symptoms.

This preliminary report is based on three cities (Fall River, Brockton and Worcester) whose original lists of reported cases totaled 3215. After the initial check, we were able to remove 929 cases because of deaths, or removals to other cities or because they could not be located in the cities. Of the 2286 cases left for reclassification, Table 1 presents the findings. Perhaps the most interesting finding is that only 22 per cent of the patients who reported to the clinic for examination were thought to require further observation. This figure is indicative of the effective reductions made

in the local lists of reported cases when we were successful in obtaining the co-operation of the patients and in getting them examined. Out of 3215 reported cases listed, only 1211, or 38 per cent, were retained on the active list, an additional 62 being kept for school clinic or contact observation.

Similar reductions are being effected in other cities and towns, and it is believed that the work of the local boards of health is being satisfactorily cut to a point where it can be handled in an easier

manner than has hitherto been possible. It is planned to report a further analysis of the material available from these studies at a later date, breaking down the statistics for pulmonary and extrapulmonary cases.

#### SUMMARY

The methods for and the results of the reclassification of reported cases of tuberculosis in three cities of Massachusetts are outlined and discussed.

## CLINICAL NOTE

### PERIPHERAL NEURITIS FOLLOWING THE ADMINISTRATION OF A GLUCOSE SULFAPYRIDINE COMPOUND\*

SAMUEL J. SUGAR, M.D.†

WASHINGTON, D. C.

**A**MONG the toxic reactions that follow the administration of sulfanilamide and its derivatives, involvement of the peripheral nerves is one of the least frequent.<sup>1</sup> This complication has been reported by various authors as occurring after the use of sulfanilamide,<sup>2,3</sup> sulfathiazole,<sup>4</sup> sulfamethylthiazole<sup>5-7</sup> and disulfanilamide.<sup>8,9</sup> Apparently, only 2 cases of peripheral neuritis after sulfapyridine have been mentioned in the literature. The first of these<sup>10</sup> is mentioned only briefly and is not fully described. The other case<sup>11</sup> was observed following the use of antimeningococcal serum and sulfapyridine, and since other signs of serum sickness appeared, the neuritis may have been due to the serum as well as to the drug.

While investigating, in a series of 60 patients with pneumonia, the therapeutic effects of glucose sulfapyridine, a crystalline compound synthesized by Dr. Lloyd D. Felton, of the National Institute of Health, I observed a case of peripheral neuritis that was apparently caused by the sulfapyridine portion of the compound. The preparation used was simply a condensation product of the aldehyde group of glucose with the amine group of the aminobenzene radical of the sulfapyridine. Analysis showed it to be a combination of one molecule of glucose with one molecule of sulfapyridine that thus required double the dosage of regular sulfapyridine to achieve similar drug intake.

#### CASE REPORT

H. G., a 23-year-old Negro, was admitted to the George Washington Medical Division of Gallinger Municipal Hospital on December 22, 1940. He had developed a cold on December 16 and the following day had noticed fever and pain in the right chest. On December 18, he became dyspneic and had a severe chill. Cough was productive of "prune-juice" sputum. There was no history of excessive indulgence in alcohol, of the use of drugs, of avitaminosis or of any neurologic disease.

Examination showed a well-developed and well-nourished young colored man who appeared acutely ill, with moderate dyspnea accompanied by an expiratory grunt. Physical examination revealed consolidation involving the upper lobe of the right lung; this was confirmed by a roentgenogram. The temperature was 102.4°F., the pulse 104, and the respirations 32. Sputum typing and a culture of the blood taken on December 24 both revealed Type 8 pneumococci. The white-cell count was 19,300, with 66 per cent polymorphonuclears, 23 per cent band forms; 3 per cent young forms and 8 per cent lymphocytes. The red-cell count was 4,520,000, with 78 per cent hemoglobin.

An initial dose of 8.0 gm. of glucose sulfapyridine was given, followed by 2 gm. every 4 hours; 1 gm. of sulfapyridine was substituted for each of two doses of glucose sulfapyridine during the 2nd day of treatment. Blood sulfapyridine levels of the drug reached 4.4 mg. per 100 cc. of free and 10.9 mg. of total sulfapyridine, 4 hours after the initial dose. Thereafter, the levels remained between 1.1 and 2.3 mg. per 100 cc. of free and between 2.2 and 5.4 mg. of total sulfapyridine, except for one rise 28 hours after the beginning of treatment to 5.0 mg. per 100 cc. free and 10.9 mg. of total sulfapyridine. The drug was discontinued on December 27 (the 6th day of treatment), after a total of 50 gm. of glucose sulfapyridine and 2 gm. of sulfapyridine had been given.

On the following day, the patient complained of numbness and tingling and difficulty in flexing the right 4th and 5th fingers. Examination revealed marked hypesthesia to pinprick over the 5th finger and the medial half of the 4th finger and over the ulnar half of the palm and dorsum as far as the wrist. There was no abnormality in ability to distinguish vibration, temperature or position. The patient was unable to distinguish the feel of wetness of water over the affected area. A diagnosis of peripheral neuritis along the distribution of the ulnar nerve was made. The symptoms and signs continued for 2 days, and the patient then left the hospital against advice. When he returned for observation 3 weeks later, all the abnormal signs and symptoms had disappeared.

\*From the George Washington Medical Division, Gallinger Municipal Hospital, Washington, D. C.

†Resident in medicine, Gallinger Municipal Hospital



Although I have seen no other case of peripheral neuritis among patients with pneumonia receiving sulfapyridine or glucose sulfapyridine, I believe that the evidence is unequivocal that the drug was the cause in the case reported. Except for a small amount of codeine and elixir of terpin hydrate, the patient received, during his hospital stay, only the glucose sulfapyridine and the sulfapyridine.

Finland and his coworkers<sup>12</sup> and Ensworth and his associates,<sup>13</sup> investigating a different glucose sulfapyridine compound, found that after absorption from the gastrointestinal tract, the glucose and sulfapyridine were separated. My own experience with the compound used in the present case coincides with this conclusion. So far as therapeutic and toxic results are concerned, sulfapyridine is therefore the only drug involved.

As the evidence accumulates, it is becoming increasingly likely that the conclusion will eventually be reached that most of the toxic manifestations that occur following any one of these drugs may sometimes occur following the use of others in the group. The variations in toxic complications following the different sulfones are therefore largely quantitative. Peripheral neuritis seems to fit into this general scheme. On the evidence of clinical reports up to the present, such neuritis is most frequent following the use of sulfamethylthiazole and disulfanilamide, is fairly often observed after the administration of sulfanilamide, and is rare following sulfathiazole. The case re-

ported suggests that this complication, although it is very rare indeed, occasionally follows the use of sulfapyridine.

### SUMMARY

A case of peripheral neuritis, with recovery, that occurred after the administration of 50 gm. of glucose sulfapyridine and 2 gm. of sulfapyridine is reported.

### REFERENCES

1. Long, P. H., and Bliss, T. A. *The Clinical and Experimental Use of Sulfanilamide, Sulfapyridine and Allied Compounds*. New York: The Macmillan Company, 1939.
2. Ornstein, A. M., and Furst, W. Peripheral neuritis due to sulfanilamide. *J. A. M. A.* 111:2103, 1939.
3. Waugh, J. R. Peripheral neuritis during administration of sulfanilamide. *Am. J. Syph., Gonorr. & Ven. Dis.* 23:745-750, 1939.
4. Bieter, R. N., Baker, A. B., Beaton, J. G., Shaffer, J. M., Seery, T. M., and Orr, B. A. Nervous injury produced by sulfanilamide and some of its derivatives in the chicken: preliminary report. *J. A. M. A.* 116:2231-2236, 1941.
5. Garvin, C. F. Peripheral neuropathy and toxic psychosis with convulsions due to sulfamethylthiazole: report of a case. *Am. J. M. Sc.* 200:362-364, 1940.
6. Solomon, S., and Kalkstein, M. Sulfamethylthiazole in the treatment of severe type II bacteremic pneumonia: report of a case treated with recovery, complicated by peripheral neuropathy. *New York State J. Med.* 41:270-272, 1941.
7. Brown, A. E., and Herrell, W. E. Clinical experience with sulfamethylthiazole. *Am. J. M. Sc.* 200:618-632, 1940.
8. Winton, R. S., and Johnson, S. H., III. Peripheral neuritis following sulfanilamide (disulfanilamide): report of four cases. *J. A. M. A.* 111:1641, 1938.
9. Hodgson, E. R. Case of peripheral neuritis following disulfanilamide treatment. *Journal-Lancet* 61:22, 1941.
10. Brown, W. H., Thornton, W. B., and Wilson, J. S. An evaluation of the clinical toxicity of sulfanilamide and sulfapyridine. *J. A. M. A.* 114:1605-1611, 1940.
11. Plügge, H. Über zentrale und periphere nervöse Schäden nach Eubasinummedikation. *Deutsche Ztschr. f. Nervenh.* 151:205-219, 1940.
12. Finland, M., Lowell, F. C., Spring, W. C., Jr., and Taylor, F. H. L. Parenteral sulfapyridine: the intravenous use of sodium sulfapyridine and a report of clinical and laboratory observations on the use of a glucose-sulfapyridine solution. *Ann. Int. Med.* 13:1105-1120, 1940.
13. Ensworth, H. K., Liebmann, J., Lockhart, M. C., and Plummer, N. Glucose-sulfapyridine: experimental and clinical studies. *Ann. Int. Med.* 15:52-62, 1941.

## MEDICAL PROGRESS

## OPHTHALMOLOGY

J HERBERT WAITE, M.D.\*

BOSTON

IT is my opinion that the work of greatest ophthalmologic interest and promise during recent years includes clinical and laboratory studies in chemotherapy and vitamin therapy, and in the pathogenesis of cataract and uveitis, and attempts to master corneal transplantation. Chemotherapy and vitamin therapy are accomplishing feats in ophthalmology that were formerly not attainable. Intensive search for the causes of cataract and uveitis—major problems in ophthalmology—has already been too long delayed. Successfully accomplished corneal grafts are salvaging the eyesight of patients heretofore considered incurably blind.

## CHEMOTHERAPY

Chinn and Bellows,<sup>1</sup> vanDyke et al.,<sup>2</sup> Spink and Hansen,<sup>3</sup> Long and Bliss,<sup>4</sup> Hill,<sup>5</sup> Rammelkamp and Keefer,<sup>6</sup> Sadusk, Blake and Seymour<sup>7</sup> and others have pioneered the way for sulfonamide therapy (sulfanilamide, sulfapyridine, sulfathiazole and sulfadiazine), with especial reference to solubility, to selective action on invading organisms, to concentration and maintenance levels in blood and tissue, to methods of increasing concentration of the drugs in avascular tissue, and to host idiosyncrasy.

The extent to which the sulfonamides reach the tissues of the eye was studied in dogs by Bellows and Chinn,<sup>8</sup> who found that the maximum drug concentration in blood and eye was reached from four to six hours after administration by stomach tube. On removal of the eyes four hours after uniform dose by stomach, and on analysis of blood and the tissues and fluids of the eye, these workers found the following distribution:

TISSUE	SULFANILAMIDE mg /100 cc or gm	SULFAPYRIDINE mg /100 cc or gm	SULFATHIAZOLE mg /100 cc or gm
Blood	18.0	6.1	7.4
Lens	2.7	1.1	0.0
Aqueous	10.9	4.9	0.9
Vitreous	8.4	5.8	2.0
Cornea	13.4	6.6	4.9
Choroid and retina	15.2	6.3	

From these observations, the authors believe that sulfathiazole is less effective in controlling intra-

ocular infection than other sulfa preparations. Scheie and Souders<sup>9</sup> reported similar findings in cats.

Using rabbits, Liebman and Newman<sup>10</sup> found it possible to increase the concentration of the sulfonamides in the aqueous by 50 per cent through repeated paracenteses, the first being made three hours after drug administration, and thereafter at thirty-minute intervals, with comparative results as follows:

DRUG	PRIMARY CONTENT OF AQUEOUS % blood conc.	SECONDARY CONTENT OF AQUEOUS % blood conc.
Sulfanilamide	67	96
Sulfapyridine	64	98
Sulfathiazole	17	41
Sulfadiazine	55	102

The increase in concentration in the aqueous is explained by the fact that the secondary fluid is a transudation from capillary blood; such an increase gives the clinician a clue to a more effective method of combating intraocular inflammation.

Caution to the point of timidity on the part of ophthalmologists has led to disappointing results in the early clinical use of sulfa drugs to control eye infections. The maintenance of blood levels of 1 to 3 mg. per 100 cc., with a correspondingly lower level in the avascular tissues of the eye, is apparently not sufficient to curb infection in ocular tissues. Mild eye infections require blood concentrations of 3 to 5 mg. per 100 cc. for five to seven days, and severe infections require levels of 6 to 12 mg. per 100 cc. for a week, as outlined by Guyton and Woods<sup>11</sup> after a careful study of 104 patients. The concentration of the drug in the blood should not exceed 20 mg. per 100 cc. on account of possible toxic effects, and effective concentration in the ocular fluids and tissues may be gained through repeated paracenteses at the peak of blood concentration.

It appears to be the consensus among careful clinicians that sulfanilamide acts more effectively for streptococcus; sulfapyridine for influenza (Koch-Weeks) bacillus, pneumococcus and meningococcus; and sulfathiazole for infections of the eye and adnexa caused by the gonococcus and

Reprints of articles in this series are not available for distribution, but the articles will be published in book form. The current volume is *Medical Progress Annual, 1940* (Springfield, Illinois: Charles C. Thomas Company, 1941) \$4.00.

\*Lecturer in ophthalmology, Harvard Medical School consultant in ophthalmology, New England Deaconess Hospital and Massachusetts Eye and Ear Infirmary.

gram-negative bacilli. *Staphylococcus*, killed in vitro by sulfathiazole in a concentration of 100 mg. per 100 cc., does not succumb to any sulfonamide level that can safely be administered to patients. Sulfonamide therapy has not proved effective in uveitis, sympathetic ophthalmia (Gamble<sup>12</sup>) or herpetic virus infections of the eyeball.

Clinical success, sometimes verging on the dramatic, has attended sulfonamide therapy in three virus diseases that consistently show basophilic heterogeneous inclusion bodies: trachoma, inclusion blennorrhea and lymphogranuloma venereum. A fourth basophilic inclusion virus, psittacosis, theoretically should succumb to sulfonamide therapy. Other virus diseases, nonvulnerable to these drugs, curiously exhibit acidophilic homogeneous inclusion bodies, according to Thygeson.<sup>13</sup> If one accepts the evidence of Julianelle et al.,<sup>14</sup> Loe<sup>15</sup> and Thygeson,<sup>16</sup> one may believe that the trachoma virus resists local applications of sulfanilamide, or blood levels below 3 to 5 mg. per 100 cc., but that it is cured by the maintenance for one week to ten days of blood levels approximating 10 mg. per 100 cc. Inclusion blennorrhea, hitherto a stubborn disease active for months under previous therapy, now, according to Thygeson,<sup>16</sup> yields in several weeks to sulfanilamide at blood levels of 3 to 5 mg. per 100 cc. Macnie<sup>17</sup> discusses the value of sulfanilamide therapy in lymphogranuloma venereum over all other known therapeutic agents.

Every patient receiving these drugs should have a daily water intake of 2500 cc., repeated blood analyses to check retention of the drug in case of renal damage, and alertness on the part of the physician for appearance of signs of idiosyncrasy. Idiosyncrasy may express itself as acidosis, nausea and vomiting, cyanosis, hematuria, skin rash, fever, hepatitis, acute hemolytic anemia or leukopenia occasionally going on to agranulocytosis and fatal outcome. The discontinuation of the drug should be guided by clinical judgment based on experience.

Sulfonamide idiosyncrasy may express itself in the visual mechanism, showing in the conjunctiva as injection and in the crystalline lens as a transitory myopia. Similar transitory refractive changes are observed in diabetes, jaundice, arsphenamine therapy, alkalosis and dehydration (Granström<sup>18</sup>). In the patient toxic from sulfonamide drugs, shifting of the refraction to myopia, frequently not observed by the patient, may evade the watchful eye of the physician unless carefully sought. Such a shift has been reported by Berns,<sup>19</sup> Spellberg,<sup>20</sup> Gailey,<sup>21</sup> Missiroli,<sup>22</sup> Blankstein,<sup>23</sup> Friedman<sup>24</sup> and Hornbogen.<sup>25</sup>

## VITAMIN THERAPY

Long misinterpreted and little understood, vitamin deficiencies such as night blindness, beriberi, pellagra, rickets, scurvy and sprue are finding explanation in the lack of sufficient vitamins in food, faulty absorption from the bowel, or faulty utilization by the cells of the body. In 1911, Casimir Funk first gave a name to the vital principle, and in 1913 Vedder and Williams<sup>26</sup> first gave proof of the reality of vitamin deficiency. Until chemical structure became known, vitamins had to parade under alphabetical aliases, the letters A to K having been given to clinically recognized vitamins, and the remaining letters to the hypothetical ones. What was formerly known as vitamin B has recently been resolved into at least twelve components, each with different qualities. Therefore, interpretation of vitamin action in the past has been chaotic, and it is just now emerging from the umbra of uncertainty as vitamin principles are synthesized, labeled with chemically descriptive names, and studied separately with respect to physiologic action, synergism and toxicity. Important examples are:

OLD NAME	NEW NAME	ACTION
A	Precursor-carotene	Antinyctalopic and antixerophthalmic
B <sub>1</sub>	Thiamine	Antineuritic
B <sub>2</sub>	Riboflavin	Promotes cell respiration
Nicotinic acid	Niacin	Antipellagrous
C	Ascorbic acid	Antiscorbutic
D	Radiated ergosterol	Antirachitic
E	Alpha tocopherol	Prevents sterility
K	Naphthoquinone	Antihemorrhagic

Salter<sup>27</sup> gives an excellent review of vitamin chemistry and current methods of assay in blood, urine and tissues. Outside the body, some vitamins are decomposed by light, and others are lost in food processing, packing and pasteurization; within the body, there is loss by abnormal excretion in colitis and polyuria, by partial destruction in achlorhydria and liver dysfunction, and by faulty absorption in steatorrhea or in too liberal use of mineral oil. Researches in vitamin chemistry, utilization and fate in the human being are awaited with keen interest by every clinician who wishes to bring his patients factual rather than empirical aid in vitamin therapy.

The advent of vitamin therapy, empirical though it has been, has brought to ophthalmology certain benefits. Yudkin<sup>28</sup> commits himself to the belief, shared by other clinicians, that an adequate vitamin A intake has reduced the incidence of phlyc-

tenuis keratoconjunctivitis, hordeol, and night blindness. Thiamine deficiency has been implicated in ophthalmoplegia and in retinobulbar neuritis. Rosacea conjunctivitis and keratitis, with stubborn and recurrent ulceration of the cornea, have been attributed to riboflavin deficiency. Thiamine and riboflavin, along with glutathione, ascorbic acid and nicotinic acid amide, are fundamental to cell respiration. They are not stored in the body, and they must be replenished daily. According to Booher,<sup>9</sup> the inadequacy of riboflavin leads to cell asphyxiation, expressing itself in the adolescent as retarded growth and in the adult as changes in the skin, changes in the central nervous system and changes in the cornea, conjunctiva and crystalline lens of the eye. The minimum requirement of riboflavin for human beings is 3 mg daily,<sup>10</sup> and it is best obtained from cow's milk, which, during the first month of lactation, contains 54 mg per quart.<sup>11</sup>

Crude thiamine and riboflavin must be converted into the phosphoric acid ester before they are acceptable for cellular oxidation and phosphorylation is thought to take place in the liver.<sup>12</sup> Carboxylase, the phosphoric acid ester of thiamine, in normal amounts acts as an antineuritic, in subnormal amounts, it arrests the oxidation of carbohydrate at the pyruvic acid stage and promotes the development of polyneuritis in the presence of toxic agents. The phosphoric acid ester of riboflavin in normal amounts, according to Veahey,<sup>13</sup> promotes cell respiration, and its absence, as shown by Bessey and Wolbach,<sup>14</sup> leads to more degenerative changes and attempts to repair by vascularization. Riboflavin does not survive gastric achlorhydria and the alkali of the duodenum. The Snell-Strong method of assay for riboflavin, although not sufficiently accurate for reliable estimate of riboflavin in vivo, capitalizes the fact that *Lactobacillus casei* *sp. nov.* cannot synthesize riboflavin and yet cannot survive without it.

Other vitamin B components — synergists and less well understood — are niacin (nicotinic acid), pantothenic acid, biotin and para-aminobenzoic acid. Deficiency of niacin leads to pellagra, with photosensitive dermatitis, keratitis and corneal ulceration, all of which are relieved by therapy with nicotinic acid amide. Georgy and Eckhardt<sup>15</sup> report that lack of pantothenic acid and biotin leads to blanching of the eyelashes and hair, and later to keratitis. Ansbacher<sup>16</sup> found that para-aminobenzoic acid inhibits the bacteriocidal action of sulfonamide.

Johnson and Eckhardt<sup>17</sup> demonstrated the healing and remission of vascularization of the cornea when the riboflavin deficit is made up. The following year, Johnson<sup>18</sup> established the chemical re-

lationship between the dermatitis conjunctivitis and keratitis of rosacea and riboflavin deficiency by rapid amelioration of signs by means of riboflavin therapy. He recommends intravenous injections for several days of 2 mg riboflavin, and concomitant oral administration of riboflavin with hydrochloric acid, since many patients with rosacea exhibit achlorhydria. After the course of treatment is completed, Johnson continues a daily riboflavin rich diet containing milk, liver and egg white. Beams, Free and Glenn<sup>19</sup> substantiate the excellent results of Johnson in the relief of rosacea keratitis through riboflavin therapy.

#### PATHOGENESIS OF CATARACT

The term *cataract*, derived when oculists were ocellists was then used to denote vision obstructed by advanced degeneration of the lens. Now, with refinements of the biomicroscope, gross covering over 100 types of lens blemishes, gross and microscopic, the same blanket term continues to be used indiscriminately, and thus to constitute one of the most flexible and most fearful words in the medical vocabulary. At the caprice of the oculist any lens blemish may be designated 'cataract', whether it is the stationary and microscopic foveal blemish within the nucleus that never obstructs vision, or the equatorial blemish of adolescence that seldom obstructs vision, or the senile radial blemish which may or may not progress after long periods of status quo or the intumescent degeneration of the entire lens with rapid decline in useful vision. For intelligent understanding between oculist, physician and hyman, the term 'cataract' should be replaced by an exact nomenclature for lens abnormalities that takes into account the lens architecture and the causation and the ultimate fate of lens abnormalities.

The crystalline lens is an island of epithelium bathed in aqueous that is a dihyalite from capillary blood, devoid of nerve or direct blood supply, surrounded by a semipermeable capsule, and provided with its own oxidation mechanism and its own protective measures for the maintenance of transparency. Its respiratory quotient is unity, its cellular oxidation and metabolism are negotiated by glutathione, ascorbic acid and riboflavin, and its water absorption is counteracted by the cholesterol content. No single theory of cataract causation encompasses or explains all known types of cataract.

The role of calcium and calcium in cataract production has been investigated by Meemann<sup>20</sup> and by von Birr.<sup>21</sup> Using the Birkler<sup>22</sup> technique for survival of the rabbit lens in vitro, von Birr demonstrated that lens changes do not follow low calcium content unless a cataractogenic substance

an unidentified protein molecule derived from hemolyzed blood, is also present. In his opinion, lens changes do not develop collaterally with human or rat rickets unless the blood calcium falls below 7 mg. per 100 cc., and unless tetany is present. In rickets, tetany is precipitated by the addition of a diet rich in phosphates, which are present in cow's milk. If tetany is transient, the lens blemish becomes zonular, and if tetany is persistent, the blemish becomes total.

Bellows and Chinn,<sup>43</sup> in fifteen papers, the last three of which were published during 1941, express the belief that the crystalline lens is a delicate osmometer, and that cataract is fundamentally the result of osmotic derangement. Paper XIII<sup>44</sup> concerns the two osmotic barriers that separate the blood from the lens cell-fiber system, and the constant interchange through these membranes of water, foodstuffs, oxygen and waste products. Paper XIV<sup>45</sup> deals with injury and altered permeability of the lens capsule and its epithelium. Paper XV<sup>46</sup> describes the swelling of the isolated lens as related to tonicity of the surrounding medium, to ionic content and hydrogen ion concentration, to temperature and to other factors.

Salit,<sup>47</sup> after a study of two hundred and fifty-nine cataractous and sclerosed lenses, removed in capsule, with reference to lipid and cholesterol content, adduces evidence that cholesterol has much to do with the water content of the lens, and that the intumescent stage of cataract is traversed by lenses that are low in the cholesterol-lipid ratio but high in total lipids.

The part played by vitamins in cataract production is suggested in the very low ascorbic acid and riboflavin content of cataractous lenses, and in the fact that the addition of adequate amounts of vitamin D to the diet in rickets and tetany prevents cataract formation.

#### PATHOGENESIS OF UVEITIS

Inflammations of the iris, ciliary body or choroid are frequently recurrent, and each attack may be accompanied by complications that endanger sight, such as glaucoma, cataract, hypotension and heavy vitreous opacities. To curb each attack and to prevent recurrences, it has become the accepted practice to make a detailed search for potential sources of uveitis throughout the body. Seldom is it possible to fulfill the postulates of Koch with respect to uveitis, and it is often impossible to demonstrate anywhere in the body what might be considered an adequate focus.

Duggan<sup>48</sup> has added the concept of tissue anoxia as a potential cause of uveitis, and he hypothesizes release of histamine locally, dilation of the uveal capillary bed, and local tissue anoxia, inflam-

mation and necrosis. He claims to be able to control this vicious circle by active vasodilator therapy, combining daily intravenous injections of 0.1 gm. of sodium nitrite with oral administration daily for two weeks of 15 to 30 mg. of erythrityl tetranitrate. Duggan also speculates on the value of a histamine ferment to destroy the noxious agent.

The search for focus applies to the paranasal sinuses, the teeth, the tonsils, the chest, the abdomen and the pelvis for the presence of pyogenic and nonpyogenic bacterial infection, and for evidence of syphilis, tuberculosis, leprosy, brucellosis and virus infection. Also, one searches for protozoan and animal parasites, which directly or through their toxins have been named as potential sources of uveitis; such parasites are *Plasmodium malariae*, *Endamoeba histolytica*, *Treponema pertenue* and *Trichinella spiralis*. Finally, one searches for allergy, particularly for the allergy from bacterial protein, tuberculo-protein and brucellar protein. The relation between arthritis and uveitis has long been recognized clinically.

Concurrence does not prove pathogenesis. From the clinical standpoint, improvement of the ocular inflammation and avoidance of ocular complications and of recurrences are the goals sought. From the standpoint of true etiology, one must be able to recover the causative agent, and to reproduce the same disease in a healthy eye. Until this requirement has been met, the pathogenesis of uveitis cannot be considered solved.

After a thoroughgoing clinical study of 244 house patients with uveitis at the Johns Hopkins Hospital, Guyton and Woods,<sup>49</sup> by clinical criteria, have allocated "causes" as follows: tuberculosis, 54 per cent; syphilis, 19 per cent; focal infection, 14 per cent; gonococcal infection, 4 per cent; and miscellaneous, 9 per cent. They do not claim that they are able to demonstrate actual micro-organisms within the infected tissues, a feat seldom accomplished in uveitis by the most meticulous staining or cultural methods. They do not report vitamin assay or virus cultures as part of their study.

#### CORNEAL TRANSPLANTATION

Nizetic<sup>50</sup> has reviewed a century of mostly unsuccessful effort to engraft healthy and clear cornea on an eye that lacks a transparent cornea, and he has outlined the contributions made by various workers.

Castroviejo<sup>51</sup> is beginning to obtain gratifying results after having performed four hundred keratoplasties on animal eyes and over two hundred keratoplasties on human eyes. His chief difficulty at present seems to be lack of donor material, rather than lack of recipients or technical difficulty

in transferring the graft. Using a double-blinded knife with blades set 4 mm. apart, the operator outlines in donor and recipient corneas a 4 mm. square, cutting through two thirds of the corneal thickness. Having used fluorescein to mark the initial incision thus made, the operator completes the incision through the cornea on one side of the square with a narrow 45°-angle keratome, cutting through the posterior third of the thickness of the cornea on a bevel. The other three sides of the square are cut through on a bevel by special scissors. Thus, the graft, 1 mm. thick and 4 mm. on each of its four sides, shows in the anterior two thirds of its thickness perpendicular sides, and in the posterior third of its thickness a 20° beveling, which prevents the graft from slipping into the anterior chamber. Formerly, the graft was held in position by a superimposed conjunctival flap. Now, the graft is held in place by a well-designed suture, which is looped over the graft from the insertion points in the adjacent peripheral cornea.

To meet the need for sufficient donor material, Castroviejo<sup>52</sup> has worked out a satisfactory method for preservation of corneal tissue in a moist chamber kept at 2°C. Thus, a cornea may be preserved for nine days free from demonstrable histologic changes. To obtain the best results, donor material is used, if possible, at once or within twenty-four hours of removal from the donor. If necessary, the operator may take four grafts of proper size outlined above from one donor cornea.

Following the lead of European workers, — notably Salzer and Magitot, — Wiener and Rosenbaum<sup>53</sup> have experimented with chemically fixed corneas from dogs and rabbits as donor material. From nine formalinized donor corneas, they report eight takes. From eight donor corneas, fixed with Ptunkowitsch's solution, they report seven takes. Healing is very slow with chemically fixed grafts, because the stroma of the graft must be replaced by the fixed cells of the recipient's cornea, and the epithelium and endothelium of the graft must be reformed from those of the recipient.

5 Bay State Road

Boston, Mass.

- 50 Scheie H. G. and S. G. P. L. The use of a double-blinded knife with blades set 4 mm. apart, the operator outlines in donor and recipient corneas a 4 mm. square, cutting through two thirds of the corneal thickness. Having used fluorescein to mark the initial incision thus made, the operator completes the incision through the cornea on one side of the square with a narrow 45°-angle keratome, cutting through the posterior third of the thickness of the cornea on a bevel. The other three sides of the square are cut through on a bevel by special scissors. Thus, the graft, 1 mm. thick and 4 mm. on each of its four sides, shows in the anterior two thirds of its thickness perpendicular sides, and in the posterior third of its thickness a 20° beveling, which prevents the graft from slipping into the anterior chamber. Formerly, the graft was held in position by a superimposed conjunctival flap. Now, the graft is held in place by a well-designed suture, which is looped over the graft from the insertion points in the adjacent peripheral cornea.
- 51 Schie H. G. and S. G. P. L. The use of a double-blinded knife with blades set 4 mm. apart, the operator outlines in donor and recipient corneas a 4 mm. square, cutting through two thirds of the corneal thickness. Having used fluorescein to mark the initial incision thus made, the operator completes the incision through the cornea on one side of the square with a narrow 45°-angle keratome, cutting through the posterior third of the thickness of the cornea on a bevel. The other three sides of the square are cut through on a bevel by special scissors. Thus, the graft, 1 mm. thick and 4 mm. on each of its four sides, shows in the anterior two thirds of its thickness perpendicular sides, and in the posterior third of its thickness a 20° beveling, which prevents the graft from slipping into the anterior chamber. Formerly, the graft was held in position by a superimposed conjunctival flap. Now, the graft is held in place by a well-designed suture, which is looped over the graft from the insertion points in the adjacent peripheral cornea.
- 52 Castroviejo J. S. Transplantation of corneal tissue in a moist chamber kept at 2°C. Thus, a cornea may be preserved for nine days free from demonstrable histologic changes. To obtain the best results, donor material is used, if possible, at once or within twenty-four hours of removal from the donor. If necessary, the operator may take four grafts of proper size outlined above from one donor cornea.
- 53 Wiener M. and Rosenbaum S. Following the lead of European workers, — notably Salzer and Magitot, — Wiener and Rosenbaum have experimented with chemically fixed corneas from dogs and rabbits as donor material. From nine formalinized donor corneas, they report eight takes. From eight donor corneas, fixed with Ptunkowitsch's solution, they report seven takes. Healing is very slow with chemically fixed grafts, because the stroma of the graft must be replaced by the fixed cells of the recipient's cornea, and the epithelium and endothelium of the graft must be reformed from those of the recipient.

## MASSACHUSETTS MEDICAL SOCIETY

## PROCEEDINGS OF THE COUNCIL

Annual Meeting, May 25 and 26, 1942

THE annual meeting of the Council of the Massachusetts Medical Society was called to order at 7:00 p.m. in the Georgian Room of the Hotel Statler, Boston, on Monday, May 25, 1942, by the president, Dr. Frank R. Ober, Suffolk; 226 councilors were present (Appendix No. 1).

The Secretary presented the record of the special meeting held on April 15, 1942, as published in the *New England Journal of Medicine*, issue of May 14, 1942. This record was approved by the Council on a motion by Dr. Walter G. Phippen, Essex South, and a second by Dr. W. Jason Mixer, Suffolk.

The following nominating councilors answered the roll call by the Secretary: W. D. Kinney, Barnstable; P. J. Sullivan, Berkshire; W. H. Allen, Bristol North; E. F. Cody, Bristol South; G. L. Richardson, Essex North; Bernard Appel, Essex South; A. G. Rice, Hampden; L. B. Pond, Hampshire; R. R. Stratton, Middlesex East; W. H. Sherman, Middlesex North; Dwight O'Hara, Middlesex South; D. D. Scannell, Norfolk; D. B. Reardon, Norfolk South; W. H. Pulsifer, Plymouth; W. B. Breed, Suffolk; R. P. Watkins, Worcester; and B. P. Sweeney, Worcester North. W. J. Pelletier, alternate member, responded for Franklin. The Committee on Nominations, so constituted, retired to deliberate.

Dr. J. Harper Blaisdell, Middlesex East, moved that if and when the annual meeting of the Council recesses it be until Tuesday, May 26, 1942, at the end of the Annual Discourse, which concludes the annual meeting of the Society. This motion was seconded by Dr. William M. Collins, Middlesex North. Dr. Blaisdell explained that this motion was offered for the purpose of giving the annual meeting of the Council the opportunity to fulfill its obligations when and if the annual meeting of the Society adopted the by-laws which were to be presented to it. This motion was unanimously adopted by the Council.

## REPORTS OF STANDING COMMITTEES

*Executive Committee*

The Secretary in presenting the report (Appendix No. 2) said that this committee had held five meetings since the stated meeting of the Council in February, 1942, and that two of these meetings were by way of hearings which were granted to the Committee on By-Laws, together with the

members of those committees likely to be affected by certain proposed changes in the by-laws. He added that one of these meetings was an all-day session and that the other lasted for five hours.

The third meeting was held on April 15, 1942. At this meeting a communication was received from Dr. Hugh F. Hare, secretary of the New England Roentgen Ray Society, expressing the desire of that organization that roentgenology and physical therapy be divorced in the sectional setup of the Massachusetts Medical Society and that a new section, to be known as the Section of Roentgenology, be established. The Executive Committee so recommended. The chairman of the Committee on Physical Therapy was acquainted with the recommendation. The Secretary then moved the adoption of this recommendation by the Council. This motion was seconded by Dr. Carl Bearse, Norfolk, and carried by vote of the Council.

The Secretary said that the fourth meeting was held on May 6, 1942. He added that Dr. Edward L. Kickham, Norfolk, was named as the choice of a special committee appointed to select a medical director for Massachusetts Medical Service and that this choice was confirmed by the Executive Committee. The Secretary moved that the Council of the Massachusetts Medical Society approve this act of the Executive Committee. This motion was seconded by Dr. George Leonard Schadt, Hampden, and so ordered by vote of the Council.

The Secretary announced that at the same meeting the Executive Committee, acting in the name of the Massachusetts Medical Society, approved of a board of directors for Massachusetts Medical Service (for personnel of the Board, see Appendix No. 2). He moved that the Council approve this act of the Executive Committee. This motion was seconded by Dr. John B. Hall, Norfolk, and so ordered by vote of the Council.

The Secretary said, for the information of the Council, that, at a meeting of the members of the Massachusetts Medical Service, all members present signed a petition for the incorporation of Massachusetts Medical Service, Mr. E. L. Twomey was elected clerk, Dr. Charles S. Butler, treasurer, and Dr. Edward L. Kickham was named as the members' choice for the medical directorship of the proposed corporation.

The Secretary spoke of an emergency session of the Executive Committee held on May 15, 1942,

at the request of Dr Reginald Fitz, chairman for the Procurement and Assignment Service in Massachusetts. He said that Dr Fitz proposed the following question:

Would the Executive Committee of the Massachusetts Medical Society be willing to recommend to the Council on Medical Education and Hospitals of the American Medical Association during the present emergency, that men from unrecognized schools who have spent four academic years of thirty-two weeks each in a school legally chartered to teach the practice of medicine who have received a diploma as a doctor of medicine from such a school, who are licensed to practice medicine in a sovereign state who have had a year's internship in a registered hospital (not necessarily one approved by the American Medical Association for intern training), and who are American citizens be eligible for commission in the armed forces with the proviso that such men be declared available for this distinction by the local and state committees for procurement and assignment in the area where they reside and on the written recommendation of five doctors in such areas who are graduates of recognized schools.

The Secretary said that the Executive Committee answered the question in the affirmative. The Secretary then moved that the Council approve this act of the Executive Committee. The motion was seconded by Dr Phippen.

Dr Reginald Fitz, Suffolk, in speaking for the adoption of the motion, said that he had recently been in Chicago and that he had placed this matter before the Council on Medical Education and Hospitals of the American Medical Association and likewise before a special committee from the American Association of Medical Colleges. He added that these groups, while friendly toward the proposition and sympathetic with its purposes felt that it was largely a local matter that should be handled by the Massachusetts Medical Society itself.

Dr John J. Curley, Worcester North, in speaking against the adoption of the motion, said that if we give unanimous support to the motion we are recommending that Middlesex men are capable and should be allowed in the armed forces of the United States. He added that we are told that graduates of approved medical schools will not volunteer. He said that he did not believe that this was so. Medical men of Massachusetts, he continued, have been waiting for the Procurement and Assignment Service to tell them when and where they are going to war and this agency has absolutely no power to tell anybody when and where they are going to war.

Dr Phippen said that, as chairman of Procurement and Assignment Service of the First Corps Area, he thought it necessary that he should talk on this subject. He spoke as follows:

I think it is incumbent upon me to say a few words. In the first place, let me say that the Procurement and Assignment Service has had the most hearty and cordial relations with the selective service board with the Surgeon General's Office of the Army and of the Navy, and with the United States Public Health Service. We are not in any argument at all with them. It is perfectly true that the Procurement and Assignment Service cannot tell a man that he should go to war and we cannot tell him he should stay out of it. All we can do is to say that he is available for military service or that he is essential to his community.

The graduates of second rate schools have presented a problem that has been very difficult to handle. The Surgeon General of the Army has already issued an edict that any graduate of a Class B medical school who is registered to practice medicine in his state who is practicing medicine in his state, who is a member of his state medical society and who can be vouched for by five graduates of an approved medical school is eligible for a commission in the Army. That edict has gone through and has been issued. The selective service boards are all cognizant of that fact. These boards do not want to induct a man who has had a medical education or any medical qualification at all into service to carry a musket. That is silly on the face of it. The Army needs doctors.

We hope that this motion will prevail. We feel that graduates of Middlesex and other second rate schools can be taken into the Army and be adequately trained in the Army and can be made efficient doctors. The Army certainly can handle these men a great deal better than we can handle them in civilian practice. And it is not sensible to leave these men behind to do all the practice left behind by graduates of first class medical schools. We sincerely hope that the Surgeon General of the Army will take these men into the service, will put them in training camps and will help to better their medical education—and we believe that he will. There is a pool of six or seven—possibly more—doctors in Massachusetts in this grade, men really needed by the service. Most of these boys want to go. I have had interviews with any number of them. They come to me and say, "Why can't I go?" I should like to go and do my share. But just because I am a graduate of a second rate school they won't let me and I don't see why I can't serve my country just as well as the graduates of a Grade A school. And he is right. He has a right to serve his country if he wants to. But we want to make that man carry a musket. It is silly. I sincerely hope that this motion will prevail. It is a problem we have considered at great length. We get very little satisfaction in talking with people who do not know anything about it. It does prevail in Illinois but not elsewhere. I sincerely hope that this motion will be carried.

Dr Herman C. Peterson, Norfolk, pointed out that, at the moment we are in a fight for our lives and that it does not make any difference whether or not we are going to be dislocated so far as our practice is concerned.

He spoke also of knowing certain graduates of nonapproved schools who were capable and ethical in their practice. He added that these men want



to do their part and they should be given some consideration.

There was a demand for the question from several sources. The motion was put by Dr. Ober, and it was so ordered by vote of the Council.

The Secretary moved the acceptance of the report of the Executive Committee as a whole. This motion was seconded by Dr. Hall and so ordered by vote of the Council.

*Committee on Membership*—Dr. G. Colket Caner, Suffolk, chairman.

This report (Appendix No. 3) was presented by Dr. Caner. It recommended that two fellows be allowed to retire, that five fellows be recommended for affiliate fellowship in the American Medical Association, two fellows be allowed to resign, that the dues of two fellows be remitted, that three fellows be allowed to change their membership from one district to another without change of legal residence and that seven fellows be recommended for readmission.

The report further recommended that the Council rescind its action of February 4, 1942, whereby it deprived Dr. George B. Coon, of Greystone Park, New Jersey, of fellowship for nonpayment of dues. Dr. Caner announced that his committee had learned that Dr. Coon died on January 18, 1941.

Dr. Fitz moved that this report and the recommendations contained therein be adopted. The motion was seconded by Dr. Phippen, and it was so ordered by vote of the Council.

*Committee on Financial Planning and Budget*—Dr. John Homans, Suffolk, chairman.

The Secretary read a letter from Dr. Homans in which he said that his committee had nothing to report.

*Committee of Arrangements*—Dr. William T. O'Halloran, Suffolk, chairman.

Dr. O'Halloran announced that Dr. Conrad Wesselhoeft, Suffolk, would take Dr. Place's spot on the scientific program tomorrow, that the annual dinner would take place in the Georgian Room instead of the Salle Moderne, that Dr. Frederick J. Lynch would act as chairman at the fourth general session on Wednesday afternoon and that the Section of Obstetrics and Gynecology had changed the place of its meeting and luncheon on Wednesday noon.

Dr. O'Halloran moved the adoption of this report as one of progress. The motion was seconded by Dr. Isaac R. Jankelson, Norfolk, and it was so ordered by vote of the Council.

*Committee on Publications*—Dr. Richard M. Smith, Suffolk, chairman.

No report.

*Committee on Ethics and Discipline*—Dr. Ralph R. Stratton, Middlesex East, chairman.

This report (Appendix No. 4) was presented by Dr. William J. Brickley, Suffolk, who said that the committee held two meetings since its last report and that it feels that a careful study of the *Code of Ethics* of the Massachusetts Medical Society and that of the American Medical Association by the fellows would lighten, to a considerable extent, the work now carried on by it.

Dr. Brickley moved the acceptance of the report. This motion was seconded by Dr. Edwin D. Gardner, Bristol South, and it was so ordered by vote of the Council.

*Committee on Medical Education*—Dr. Robert T. Monroe, Norfolk, chairman.

The report (Appendix No. 5) was offered by Dr. Monroe. He said that his committee had held two meetings. At the two meetings, 53 graduates of foreign medical schools were considered, of whom 31 (59 per cent) were accepted, as compared with 92 last year, of whom 64 (69 per cent) were accepted. The prediction that the number of applicants from foreign schools would decrease has proved true so far. Also, 87 graduates of unapproved domestic medical schools were considered, of whom 49 (56 per cent) were accepted. This compares with 80 a year ago, of whom 27 (33 per cent) were accepted. There seems to be no change in the number of applicants from these schools, and in general the local boards of membership found in their favor more often than they have done in the past. During the year only 130 graduates of approved schools applied, or 10 less than the number in the other two categories. Some of this falling off may be attributed to the claims of the armed forces on these men. However, the continued decrease, both in numbers and proportions, of graduates of Class A schools seeking membership in the Society is a source of real concern to the committee and merits serious study. Dr. Monroe added that a list of medical schools approved by the committee was appended to the report.

Dr. Monroe moved that the report be accepted. This motion was seconded by Dr. Phippen, and it was so ordered by vote of the Council.

*Committee on State and National Legislation*—Dr. Henry C. Marble, Suffolk, chairman.

This report (Appendix No. 6) was offered by Dr. Marble, who moved its acceptance. This mo-

ion was seconded by Dr Richard M Smith, Suffolk, and it was so ordered by vote of the Council

*Committee on Public Health*—Dr Francis P Denny, Norfolk, chairman

No report

*Committee on Medical Defense*—Dr Arthur W Allen, Suffolk, chairman

The report\* was read by Dr Allen. It reads as follows:

There are at present seven cases pending. During the past year, two cases have been successfully disposed of—one being dismissed for lack of prosecution and the other having been carried to the Supreme Judicial Court after a trial judge had directed a verdict for the defendant in the proceedings of 1940. The Supreme Judicial Court upheld the action of the trial judge.

One new case has been accepted for defense during the past year.

Since many of our fellows are going into military service, the question has been raised regarding the possibility of lawsuits while on active duty. We have obtained an opinion from our attorneys regarding this point and quote in part as follows:

It would seem to me that it would be desirable for members of the medical profession who are in the United States Army or Navy to proceed on the assumption that there might be liability for negligent treatment. In the first place, the law is not clear. In the second place, whether or not there can be a recovery against a man in these circumstances, he cannot prevent suits being brought against him and, if suit is brought, he is put to the expense of engaging a lawyer to defend him. Furthermore, although he is in the Army and engaged in his army duties most of the time, he may be called upon under some circumstances to treat someone who is a civilian in which case there is no doubt that he is liable for negligence. It should be borne in mind that the fact that a doctor is not paid by his patient for the treatment he renders has no bearing on the question whether or not the doctor can be sued. I would therefore recommend that those members of the medical profession who have in the past carried malpractice insurance should in order to be on the safe side continue to do so while they are in the military service.

The above opinion is in accordance with editorials on the subject in the *Journal of the American Medical Association*, page 936, issue of September 13, 1941, and in the *New England Journal of Medicine*, page 700, issue of April 23, 1942.

It seems to the committee that this recommendation by our attorneys regarding our members and their malpractice insurance should apply also to the members who do not carry malpractice insurance. In members who do not carry malpractice insurance, the fact that they remain members in good standing while in military service without the payment of dues, may cause them to be careless about re-establishing their status in the Society when they are released from military service. It is recommended therefore that all members be careful to make known their return to a

civilian status as soon as they are discharged from military service since it is necessary for them to be members in good standing at the time of an alleged malpractice if they are to benefit from the legal support given by the Society under such circumstances.

Dr Allen moved the acceptance of the report and the adoption of the recommendations contained therein. The motion was seconded by Dr Hall, and it was so ordered by vote of the Council.

*Committee on Permanent Home*—Dr William H Robey, Suffolk, chairman

Dr Robey reported as follows:

At a meeting of the Committee on Permanent Home held on May 13, 1942, it was voted that it is inadvisable at present for the Massachusetts Medical Society to purchase and furnish a building to be used as a headquarters house. Recently we have considered two buildings, one quite near the Boston Medical Library and one quite remote from it but neither would be satisfactory. From time to time I have discussed this problem with members living in and out of Boston, and I have yet to find any member who has expressed the slightest enthusiasm over such a project. It would be difficult to secure at present any space which would be superior to what we have now in the Boston Medical Library. Later, even more space may be available in the library building.

The *New England Journal of Medicine* is satisfactorily located in the library building and the editors find the library a very necessary adjunct. All bibliographical references cited in manuscripts are checked in the library before publication.

Many of us would deplore a separation of the Society from the library and believe that the Massachusetts Medical Society should do all in its power to assist the Boston Medical Library, which, as many of us know, is the fourth in importance in the United States.

Dr Robey moved that the decision of his committee be accepted. This motion was seconded by Dr David Cheever, Suffolk, and it was so ordered by vote of the Council.

Dr Robey moved that the President appoint a committee of five members, one of whom shall be the Treasurer of the Massachusetts Medical Society, to see if anything can be done by the Society to help the Boston Medical Library. This motion was seconded by Dr Albert A Hornor, Suffolk, and it was so ordered by vote of the Council.

#### REPORTS OF SPECIAL COMMITTEES

*Committee on Cancer*—Dr Shields Warren, Suffolk, chairman

No report

*Committee on Public Relations*—Dr Elmer S Bignall, Essex North, secretary

No report

*Committee on Tax-Supported Medical Care*—Dr Bignall, chairman

\*This report is here reproduced in toto because of its great importance to members of the Massachusetts Medical Society.

The report (Appendix No. 7) was offered by Dr. Bagnall, who moved its adoption. The motion was seconded by Dr. Horner, and it was so ordered by vote of the Council.

*Committee Concerned with Prepayment Medical-Care Costs Insurance*—Dr. James C. McCann, Worcester, chairman.

No report.

*Committee Concerned with Postpayment Medical-Care Costs through Banks*—Dr. Bagnall, chairman.

Dr. Bagnall read the report (Appendix No. 8). This report recommended that this plan be adopted in principle, the details to be worked out by the Committee on Public Relations and initiated when completed.

Dr. Bagnall moved the adoption of the recommendation. This motion was seconded by Dr. Gardner.

Dr. Schadt inquired how this scheme compares with the method of financing offered by the Morris Plan. Dr. Bagnall said that the Morris Plan group of banks in this area vary in their interest charges. He added that he had in his book some of the rates of interest charged for carrying these loans and that none were anywhere near as favorable as this one.

Dr. Ober put the motion, and it was carried by vote of the Council.

*Committee on Postgraduate Instruction*—Dr. Reginald Fitz, Suffolk, chairman.

Dr. Fitz, in reading the report (Appendix No. 9), said that interest in postgraduate study had met a great distraction—the war. He added that in 1941-1942 twelve districts did not have any course, while nine continued with greatly reduced enrollment. He complimented the faculty on the excellence of its service.

He said that the Executive Committee and Program Committee of the New England Postgraduate Assembly, at a meeting held on May 12, 1942, had voted to postpone the assembly for the duration. He added that this decision met with the approval of the other New England state medical societies.

He finally announced that the committee is studying the problems of postgraduate instruction in the field of industrial medicine, particularly those related to defense industries, and that an announcement concerning this would appear in the *New England Journal of Medicine* during the summer.

He moved the adoption of the report. This motion was seconded by Dr. Petterson, and it was so ordered by vote of the Council.

*Committee on Physical Therapy*—Dr. Franklin P. Lowry, Middlesex South, chairman.

Dr. Lowry said in this report (Appendix No. 10) that there are four excellent schools for training physical therapy technicians in Greater Boston. He added that there are also several other schools operated largely from a commercial viewpoint. He added that the training which the latter give is superficial. An article pertaining to the selection of schools for the training of physical therapy technicians is to be printed in *Massachusetts Teacher*, a publication that reaches 27,000 teachers. Dr. Lowry stated that he believed that this article would be of special help to those concerned with vocational guidance.

He moved the adoption of the report. This motion was seconded by Dr. Schadt, and it was so ordered by vote of the Council.

*Committee to Consider Expert Testimony*—Dr. George Leonard Schadt, Hampden, chairman.

This report (Appendix No. 11), offered by Dr. Schadt, spoke of the difficulties that the committee had encountered since its creation in 1936, in consequence of which not very much has been accomplished.

Dr. Schadt moved the adoption of the report. This motion was seconded by Dr. Gardner.

Dr. Ober, in this connection, spoke of a talk on this subject that he gave last winter before the Massachusetts Law Society. He added that the officers of that society promised that a committee would be appointed to collaborate with the committee of this Society. He pointed to Minnesota as evidence of how fruitful such collaboration might be.

The motion was adopted by vote of the Council.

*Committee on Industrial Health*—Dr. W. Irving Clark, Worcester, chairman.

No report.

Dr. Ober referred to three March issues of the *Journal of the American Medical Association*, which outline the functions of such a committee. He added that we should work with the Industrial Health Council of the American Medical Association.

*Committee on Army Medical Library and Museum*—Dr. Henry R. Viets, Suffolk, chairman.

No report.

*Committee to Examine WPA Records*—Dr. Guy L. Richardson, Essex North, chairman.

Dr. Richardson spoke in this report (Appendix No. 12) of the reduced number of WPA accidents consequent on the decreased employment under this auspices. He added that the State Compen-

sation Officer felt that this committee had been of immeasurable help in adjusting unreasonable charges and claims

He moved the adoption of the report This motion was seconded by Dr William E Browne, Suffolk, and it was so ordered by vote of the Council

*Committee on Maternal Welfare*—Dr Judson A Smith, Suffolk, chairman

No response

*Committee on Rehabilitation*—Dr William E Browne, Suffolk, chairman

Dr Browne in this report (Appendix No 13) spoke of the several steps that the committee had taken to make the Massachusetts Medical Society of help to the selective service officials in the matter of the rehabilitation of rejected selectees He added that Colonel Donald E Currier, of the Massachusetts Selective Service System, had expressed his willingness to use the machinery of the district medical societies in determining the qualifications of certain doctors suggested by various selective service boards throughout the state and by others

Dr Browne asked the Council to approve the action of the Committee on Rehabilitation in insuring those in charge of selective service boards in Massachusetts that the various district medical societies and the Massachusetts Medical Society as a whole would co-operate in this matter

Dr Browne moved that the action of the Rehabilitation Committee be approved This motion was seconded by Dr William M Collins Middlesex North, and it was so ordered by vote of the Council

*Committee to Study the Practice of Medicine*—Dr Dwight O Harr, Middlesex South, chairman

No report

*Committee of One to Visit Various State Aided Cancer Clinics*—Dr Channing C Simmons Suffolk

No response

*Committee on Procurement and Assignment\**—Dr Reginald Fitz, Suffolk, chairman

Dr Fitz read his report (to be published as an original article in the July 2 issue of the *Journal*) and moved its acceptance The motion was seconded by Dr Charles F Wilinsky, Suffolk

Dr Carl Berse, Norfolk, asked the following question, "Inasmuch as the draft age is forty five, what is the necessity for selecting the figure forty two years?" Dr Fitz, by way of answering this question, stated that the Surgeon General of the

Army has said, over and over again, that what they want are a certain number of men of the rank of a first lieutenant, a smaller number of men of the rank of captain, a fewer number still of the rank of major and practically no lieutenant colonels or colonels It has been found out by past experience that a man who is forty five years old has to be given a rank higher than lieutenant because he will not do the job of lieutenant so well as a younger man Therefore, they are trying to get the younger men first, and then they will go later to this older group if they cannot obtain the necessary number of younger men that they so vitally need

Dr Raymond A McCarty, Middlesex South asked if a man who has been cleared by the Procurement and Assignment Service is notified by this agency provided he has already volunteered Dr Fitz replied that, as Dr Curley brought out earlier, the Procurement and Assignment Service should carry a man until that man volunteers, so that in any district a man must be cleared by Washington before he can volunteer for service

Dr Fitz's motion to adopt the report was carried by vote of the Council Dr Fitz was granted permission to present this report to the third general session of the Society on Wednesday morning, May 27

### *Committee on Nominations*

Dr Guy L Richardson Essex North, reported for the committee the following list of officers

For president elect Roger I Lee Suffolk  
For vice president Peirce H Leavitt Plymouth  
For secretary Michael A Tighe Middlesex North  
For treasurer Charles S Butler Suffolk  
For orator Edward P Bagg Hampden

These nominations were greeted with applause

Dr Ober asked for nominations from the floor There were none Dr Berse moved that the nominations be closed Dr Fitz seconded the motion, and it was so ordered by vote of the Council

Dr Wilinsky moved that the Secretary be instructed to cast one ballot bearing the names submitted by the Committee on Nominations This motion was seconded by Dr Jankelson, and it was so ordered by vote of the Council The Secretary announced that he had complied with this direction

Dr Ober declared amid great applause these men elected

### NEW BUSINESS

President Ober announced his nominations for the various standing and special committees for 1942 and 1943 These nominations were confirmed

\*This is not a committee of the Massachusetts Medical Society as such, but a committee of the Society to study the problem of selective service.

by vote of the Council. (The list will be published with the proceedings of the Society in the July 9 issue of the *Journal*.)

Dr. Ober announced the death of two councilors.

Dr. Charles H. Dalton, of Somerville, died February 12. He was in his sixty-sixth year.

Born in Charlottetown, Prince Edward Island, Dr. Dalton received his degree from McGill University Faculty of Medicine in 1901. He was on the staff of the Somerville Hospital, and was a fellow of the American Medical Association.

He is survived by his widow and five sisters.

On motion of the Secretary the Council stood in silence for one minute in tribute to the memory of Dr. Dalton.

Dr. William J. Delahanty, of Worcester, died May 10. He was in his eighty-fifth year.

A native of Fitchburg, Dr. Delahanty received his degree from Dartmouth Medical School in 1883. He was an incorporator and a member of the staff of St. Vincent's Hospital, and was on the staff of the Worcester City Hospital for more than fifty years. He was a trustee of the Worcester State Hospital, and was a fellow of the American Medical Association.

On motion of the Secretary, the Council stood in silence for one minute in tribute to the memory of Dr. Delahanty.

Dr. Ober read a communication from the Woman's Auxiliary of the American Medical Association asking that a branch of this auxiliary be set up in Massachusetts. The Secretary moved that the communication be referred to the Executive Committee with the idea of having this committee explore the possibilities of setting up a woman's auxiliary in Massachusetts as part of the Woman's Auxiliary of the American Medical Association. This motion was seconded by Dr. Phippen, and it was so ordered by vote of the Council.

The Secretary presented two nominations for honorary fellowship in the Massachusetts Medical Society: Dr. Carl R. Doering — sponsored by Dr. Eliot Hubbard, Jr., Middlesex South, and Dr. Hilbert F. Day, Middlesex South — and Dr. Walter F. Dearborn — sponsored by Dr. Fabyan Packard, Middlesex South, and Dr. Day. Dr. Day moved that these nominations be referred to the Committee on Membership. This motion was seconded by Dr. Richard M. Smith, Suffolk, and it was so ordered by vote of the Council.

Dr. Ober read a communication from the Hampden District Medical Society inviting the Massachusetts Medical Society to hold its next annual meeting in Springfield. Dr. George A. Moore, Plymouth, moved that the invitation be accepted. This motion was seconded by Dr. Charles C. Lund, Suffolk, and it was so ordered by vote of the Council.

The Secretary presented two certificates for membership in the Massachusetts Medical Society irregularly certified by two boards of censors. He explained that the fault in both these cases lay in the nonobservance of Chapter V, Section 2 (a), as this section relates to the timetable governing the admission of graduates of approved medical schools to the Massachusetts Medical Society. The applications were received too late and they were not advertised in the *Journal*. Dr. H. Quimby Gallupe, Middlesex South, said that this matter was discussed in the meeting of the supervising censors held earlier in the day. He added that he was a member of one of the boards of censors certifying one of these candidates and that his board had so acted because it wanted some definite decision in the matter by the Council. This decision would guide his board and all other boards when and if similar circumstances arose. He pointed out that it would be very difficult for doctors entering the service to be promoted if they were not members of their state societies. He said there was a disposition among the supervising censors to facilitate such admissions in the case of graduates of approved schools. With this thought in mind, he offered the following motion:

The supervising censors recommend that Chapter V, Section 2 (a), of the by-laws of the Massachusetts Medical Society, as this section relates to the timetable governing graduates of approved schools in their applications for membership in the Massachusetts Medical Society, be waived, in the interest of those who are either in or who contemplate entering the armed forces of our country and that this regulation shall prevail for the period only of the present emergency.

This motion was seconded by Dr. Petterson.

Dr. Charles E. Mongan, Middlesex South, in seeking information, asked if this motion were passed would the by-laws of the Society be thereby nullified or amended. There was a great deal of debate following Dr. Mongan's question, in which Dr. Petterson, Dr. Frothingham, Dr. Collins, Dr. Mongan, Dr. George C. Tully, Worcester, Dr. W. A. R. Chapin, Hampden, Dr. Cheever, Dr. Fitz, Dr. Denny, Dr. Hornor, Dr. Schadt, Dr. Browne and Dr. Bagnall participated.

Dr. Ober inferentially answered Dr. Mongan's question in the affirmative, by ruling Dr. Gallupe's motion out of order. Some informal discussion continued on the subject. Dr. Ober informed the Council that he would consult counsel and report to the Council the following day, at the recessed meeting, the results of such consultation.

The Secretary moved that the Council postpone action on the two irregular certificates until the

recessed meeting of the Council This motion was seconded by Dr. Mongin, and it was so ordered by vote of the Council.

Dr. Ober called on the Secretary to read a letter that concerned the approving authority for schools for nurses (Appendix No 14). Dr. Mongin moved that this communication be referred to the Committee on Medical Education The motion was seconded by Dr. Horace P. Stevens, Middlesex South, and it was so ordered by vote of the Council

At this point, 10:30 p. m., the annual meeting of the Council recessed until Tuesday, May 26, 1942

\* \* \*

The annual meeting of the Council reconvened at 2-45 p. m., Tuesday, May 26, 1942, in the Salle Moderne, Hotel Statler, Boston. Dr. Ober presiding.

Dr. Ober called on the Committee on Nominations for a nomination for the office of assistant treasurer. Dr. Guy L. Richardson, reporting for this committee, named Dr. Eliot Hubbard, Jr. Dr. Ober called for nominations from the floor. There were none. Dr. Hornor moved that the nominations be closed. This motion was seconded by Dr. Fitz, and it was so ordered by vote of the Council. Dr. Smith moved that the Secretary cast one ballot for assistant treasurer bearing the name of Dr. Eliot Hubbard, Jr. The Secretary announced that this direction had been complied with. Dr. Ober declared Dr. Eliot Hubbard, Jr., assistant treasurer of the Massachusetts Medical Society for the year 1942-1943.

Dr. J. Harper Blaisdell, Middlesex East, moved that the councilors elected in 1942 shall continue to serve in 1943 until after the annual meeting of the Society. This motion was seconded by Dr. Hornor, and it was so ordered by vote of the Council, after the Secretary had explained that under the new by-laws the councilors elected by the districts in 1943 would not take office until after the annual meeting of the Society in 1943.

Dr. Ober submitted his nominations for the newly created Committee on Industrial Health. The list will be published with the proceedings of the Society in the July 9 issue of the *Journal*. The confirmation of these nominations was moved by Dr. Smith. This motion was seconded by Dr. Fitz, and it was so ordered by vote of the Council.

The Secretary again called the Council's attention to the two irregular certifications for membership in the Massachusetts Medical Society, action on which had been postponed earlier in the annual meeting of the Council. He moved, in view

of the action of the annual meeting of the Society, that these men be declared members of the Massachusetts Medical Society. This motion was seconded by Dr. Walter H. Pulsifer, Plymouth, and it was so ordered by vote of the Council.

Dr. Ober announced that the business on the docket had been completed. Dr. Blaisdell moved adjournment. The motion was seconded by Dr. Pulsifer, and on a vote, the Council adjourned at 2:55 p. m.

MICHAEL A. TIGHE, *Secretary*

# APPENDIX NO 1

## ATTENDANCE

Council Meeting—May 25, 1942

BARNSTABLE	J. W. Trask
W. D. Kinney	C. A. Worthen
BIRKSHIRE	FRANKLIN
I. S. T. Dodd	H. L. Craft
Solomon Schwager	W. J. Pelletier
P. J. Sullivan	
BRISTOL NORTH	HAMPDEN
W. H. Allen	F. H. Allen
J. H. Brewster	W. C. Barnes
J. L. Murphy	W. A. R. Chapin
BRISTOL SOUTH	G. B. Corcoran
C. A. Bonney, Jr.	*S. C. Cox
R. B. Butler	A. J. Douglas
E. F. Cody	E. C. Dubois
E. D. Gardner	P. E. Gerr
H. E. Perry	Frederic Hygler
P. E. Truesdale	G. D. Henderson
ESSEX NORTH	E. A. Knowlton
E. G. Bignall	M. W. Pearson
R. V. Bicketel	A. G. Rice
L. R. Chaput	G. L. Schadt
J. P. Creed	
H. R. Kurth	HAMPSHIRE
P. J. Look	A. J. Bonneville
R. C. Norris	R. S. Clapp
G. L. Richardson	J. R. Hobbs
D. W. Wallwork	L. B. Pond
C. F. Warren	
ESSEX SOUTH	MIDDLESEX EAST
Bernard Appel	J. H. Blaisdell
H. A. Boyle	Richard Dutton
C. P. Brown	E. M. Halligan
D. S. Clark	J. H. Kerrigan
C. L. Curtis	K. L. Macfachlan
R. E. Foss	M. J. Quinn
P. P. Johnson	R. R. Stratton
A. F. Parkhurst	
O. S. Pettingill	MIDDLESEX NORTH
W. G. Plummer	M. L. Alling
H. G. Pope	H. R. Coburn
C. D. Reynolds	W. M. Collins
J. R. Shaughnessy	D. J. Ellison
	A. R. Gardner
	W. H. Sherman
	M. A. Tighe

## MIDDLESEX SOUTH

C. F. Atwood  
E. W. Barron  
Harris Bass  
J. M. Baty  
E. H. Bigelow  
W. O. Blanchard  
G. F. H. Bowers  
R. W. Buck  
E. J. Butler  
H. F. Day  
C. L. Derick  
\*D. C. Dow  
J. G. Downing  
C. W. Finnerty  
H. Q. Gallupe  
F. W. Gay  
H. G. Giddings  
H. W. Godfrey  
A. D. Guthrie  
R. D. Halloran  
Eliot Hubbard, Jr.  
L. H. Jack  
A. M. Jackson  
A. A. Levi  
F. P. Lowry  
A. N. Makechnic  
R. A. McCarty  
Dudley Merrill  
C. E. Mongan  
J. P. Nelligan  
S. J. G. Nowak  
E. J. O'Brien, Jr.  
Dwight O'Hara  
L. G. Paul  
Max Ritvo  
E. H. Robbins  
M. J. Schlesinger  
E. F. Sewall  
E. W. Small  
H. W. Thayer  
A. B. Toppan  
J. E. Vance  
B. M. Wein  
M. W. White  
Hovhannes Zovickian

## NORFOLK

J. R. Barry  
Carl Bearse  
Arthur Berk  
M. I. Berman  
William Dameshek  
F. P. Denny  
Susannah Friedman  
David Glunts  
B. T. Guild  
D. L. Halbersleben  
J. B. Hall  
R. J. Heffernan  
I. R. Jankelson  
H. L. Johnson  
C. J. Kickham  
E. L. Kickham  
D. L. Lionberger  
D. S. Luce  
C. M. Lydon  
D. L. Lynch  
T. F. P. Lyons  
Charles Malone  
F. P. McCarthy

## R. T. Monroe

F. J. Moran  
Hyman Morrison  
M. W. O'Connell  
H. C. Petterson  
S. A. Robins  
S. M. Saltz  
D. D. Scannell  
J. A. Seth  
Kathleyn S. Snow  
J. W. Spellman  
J. P. Treanor, Jr.  
W. J. Walton  
N. A. Welch

## NORFOLK SOUTH

C. S. Adams  
F. A. Bartlett  
H. H. A. Blyth  
F. W. Crawford  
D. B. Reardon  
H. A. Robinson

## PLYMOUTH

J. E. Brady  
Charles Hammond  
W. T. Hanson  
C. D. McCann  
G. A. Moore  
W. H. Pulsifer

## SUFFOLK

H. L. Albright  
A. W. Allen  
H. L. Blumgart  
W. B. Breed  
W. J. Brickley  
W. E. Browne  
C. S. Butler  
G. C. Caner  
E. M. Chapman  
David Cheever  
Pasquale Costanza  
R. L. DeNormandie  
G. B. Fenwick  
Reginald Fitz  
Maurice Fremont-Smith  
Channing Frothingham  
Joseph Garland  
A. A. Horner  
C. S. Keefer  
H. A. Kelly  
R. I. Lee  
C. C. Lund  
H. C. Marble  
W. J. Mixer  
H. L. Musgrave  
R. N. Nye  
F. R. Ober  
W. T. O'Halloran  
J. P. O'Hare  
L. E. Parkins  
L. E. Phaneuf  
W. H. Robey  
R. M. Smith  
E. F. Timmins  
S. N. Vose  
Shields Warren  
Conrad Wesselhoeft  
C. F. Wilinsky

## WORCESTER

J. C. Austin  
L. R. Bragg  
P. H. Cook  
G. A. Dix  
L. M. Felton  
E. R. Leib  
W. F. Lynch  
J. C. McCann  
A. E. O'Connell  
R. S. Perkins

\*Deceased.

J. J. Tegelberg  
G. C. Tully  
R. J. Ward  
F. H. Washburn  
R. P. Watkins

## WORCESTER NORTH

E. A. Adams  
J. J. Curley  
C. B. Gay  
B. P. Sweeney

## APPENDIX NO. 2

## REPORT OF THE EXECUTIVE COMMITTEE

The Executive Committee has had five meetings since the stated meeting of the Council in February.

The February 25 and March 4 meetings represented hearings which were given to the Committee on By-Laws; present likewise at these hearings were the committees likely to be affected by proposed changes in the by-laws. One of these meetings was an all-day session and the other lasted for five hours.

The third meeting was held on April 15, 1942. The committee was in receipt of a communication from Dr. Hugh F. Hare, secretary of the New England Roentgen Ray Society, expressing the desire of that organization that radiology be divorced from the Section of Radiology and Physiotherapy and that a separate Section of Roentgenology be set up. The committee so recommended. The chairman of the Committee on Physical Therapy was informed of this action.

The meeting of May 6 was concerned with the organization of Massachusetts Medical Service.

At the stated meeting of the Council, February 4, 1942, the following recommendation of the Committee on Prepayment Medical-Care Costs Insurance was adopted: "That a special committee be appointed by the Executive Committee to select an executive director." (The reference is to a medical director of Massachusetts Medical Service.)

Dr. Peirce H. Leavitt, chairman of the committee appointed by Dr. Ober under this direction, reported that Dr. Edward L. Kickham, of Norfolk, was the unanimous choice of this committee for the position. Dr. Kickham is a resident of Brookline where he was born November 6, 1895. He enlisted in the armed forces of our country in May, 1917, as a private—interrupting his college course to do so. He was honorably discharged December, 1918, a lieutenant in the infantry. He was graduated from Boston College in 1919 and Tufts College Medical School in 1923. He interned at the Carney and New York Lying-In hospitals. He has practiced his profession in Boston since. He is a fellow of the American College of Surgeons and a diplomate of the American Board of Obstetrics and Gynecology. He is a member of the staffs of St. Elizabeth's and Carney hospitals. He is an instructor in gynecology at Tufts College Medical School and assistant surgeon at the New England Medical Center. He is a member of the Massachusetts Medical Society and has been a councilor to the body from the Norfolk District for several years. He holds membership in the American Medical Association and the New England Gynecological and Obstetrical and the Boston Obstetrical societies.

The choice of Dr. Kickham for this position was approved by the Executive Committee.

## LOUISIANA

Louisiana State University School of Medicine, New Orleans.  
Tulane University of Louisiana School of Medicine, New Orleans.

## MARYLAND

Johns Hopkins University School of Medicine, Baltimore  
University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore.

## MASSACHUSETTS

Boston University School of Medicine, Boston  
Harvard Medical School, Boston.  
Tufts College Medical School, Boston.

## MICHIGAN

University of Michigan Medical School, Ann Arbor  
Wayne University College of Medicine, Detroit

## MINNESOTA

University of Minnesota Medical School, Minneapolis.

## MISSOURI

St. Louis University School of Medicine, St. Louis  
Washington University School of Medicine, St. Louis

## NEBRASKA

Creighton University School of Medicine, Omaha  
University of Nebraska College of Medicine, Omaha

## NEW YORK

Albany Medical College, Albany.  
Long Island College of Medicine, Brooklyn.  
University of Buffalo School of Medicine, Buffalo.  
Columbia University College of Physicians and Surgeons, New York.  
Cornell University Medical College, New York.  
New York Medical College, Flower and Fifth Avenue Hospitals, New York.  
New York University College of Medicine, New York.  
University of Rochester School of Medicine and Dentistry, Rochester.  
Syracuse University College of Medicine, Syracuse.

## NORTH CAROLINA

Duke University School of Medicine, Durham

## OHIO

University of Cincinnati College of Medicine, Cincinnati  
Western Reserve University School of Medicine, Cleveland.  
Ohio State University College of Medicine, Columbus.

## OKLAHOMA

University of Oklahoma School of Medicine, Oklahoma City.

University of Oregon School of Medicine, Portland

Hospital of Philadelphia, Philadelphia.  
Phil.

University of Pennsylvania School of Medicine, Philadelphia.  
Woman's Medical College of Pennsylvania, Philadelphia.  
University of Pittsburgh School of Medicine, Pittsburgh.

## SOUTH CAROLINA

Medical College of the State of South Carolina, Charleston.

## TENNESSEE

University of Tennessee College of Medicine, Memphis.  
Meharry Medical College, Nashville.  
Vanderbilt University School of Medicine, Nashville.

## TEXAS

Baylor University College of Medicine, Dallas.  
University of Texas Faculty of Medicine, Galveston.

## VERMONT

University of Vermont College of Medicine, Burlington.

## VIRGINIA

University of Virginia Department of Medicine, Charlottesville.  
Medical College of Virginia, Richmond

## WISCONSIN

University of Wisconsin Medical School, Madison.  
Marquette University School of Medicine, Milwaukee.

## CANADA

University of Alberta Faculty of Medicine, Edmonton, Alberta  
University of Manitoba Faculty of Medicine, Winnipeg, Manitoba.  
Dalhousie University Faculty of Medicine, Halifax, Nova Scotia  
Queen's University Faculty of Medicine, Kingston, Ontario  
University of Western Ontario Medical School, London, Ontario  
University of Toronto Faculty of Medicine, Toronto, Ontario  
McGill University Faculty of Medicine, Montreal, Quebec.  
University of Montreal Faculty of Medicine, Montreal, Quebec.  
Laval University Faculty of Medicine, Quebec, Quebec.

## APPENDIX NO 6

## REPORT OF THE COMMITTEE ON STATE AND NATIONAL LEGISLATION

Since the last report of this committee in the fall of 1941, there has been no session of the Massachusetts Legislature that has considered any bills of concern to this society. In the Capitol, the present emphasis is on the conduct of the war. There are many bills pending that so far have remained dormant. These bills concern health insurance, hospitalization, social security and medical care. There are also bills relative to the administration of public health. All these bills are being followed by the several interested bodies in Washington. After the present crisis, surely many of these bills will be revised and require much study and consideration.

HENRY C. MARBLE, Chairman  
EAPLE M. CHAPMAN  
BRINARD F. CONLEY



Atkinson, Velma H., Foxboro  
 Ciani, A. Walter, Cambridge  
 Gosline, Harold I., Arlington Heights  
 Marcellino, Samuel E., Milton  
 McCready, L. T., Jamaica Plain  
 McLeod, Melvin S., Melrose  
 Taylor, Edward H., Swansea

7. That the Council rescind its action of February 4, 1942, whereby it deprived of fellowship for nonpayment of dues George B. Coon, of Greystone Park, New Jersey. (The committee has recently learned that Dr. Coon died on January 18, 1941. Previous to that time he had been an esteemed fellow of the Society for many years.)

G. COLKET CANER, *Chairman*

#### APPENDIX NO. 4

##### REPORT OF THE COMMITTEE ON ETHICS AND DISCIPLINE

The major portion of the year's work of the Committee on Ethics and Discipline was reported on February 4, 1942, to the Council and will be found under Appendix No. 8 (page 434) in the March 12, 1942, issue of the *New England Journal of Medicine*.

Subsequent to that meeting the committee has held two full-day meetings, discussing and settling cases which fell into the different classes noted in our previous report.

The committee feels that a careful study of the *Code of Ethics* of the Massachusetts Medical Society and that of the American Medical Association by the fellows would lighten, to a considerable extent, the work now carried on by it.

WM. J. BRICKLEY

ALLEN G. RICE

FRED R. JOUETT

ARCHIBALD R. GARDNER

RALPH R. STRATTON, *Chairman*

#### APPENDIX NO. 5

##### REPORT OF THE COMMITTEE ON MEDICAL EDUCATION

Two regular meetings were held before the November and May censors' examination of candidates for admission to the Society, and the qualifications of the candidates from foreign medical schools and from unapproved domestic schools were studied. In the very great majority of cases the decisions were in agreement with those of the local boards of membership. Most of the disagreements were settled to the satisfaction of each committee. It is the committee's belief that the local boards are doing their work well, upholding the interest of the Society, as well as those of the candidates. It is also our feeling that most of the boards welcome a review of their decisions by a committee of the Society. Under the new by-laws, this work will henceforth be in charge of the Committee on Membership.

At the two meetings, 53 graduates of foreign medical schools were considered, of whom 31 (59 per cent) were accepted, as compared with 92 last year of whom 64 (69 per cent) were accepted. The prediction that the number of applicants from foreign schools would decrease has proved true so far. Also, 87 graduates of unapproved domestic medical schools were considered, of whom 49 (56 per cent) were accepted. This compares with 80 a year ago, of whom 27 (33 per cent) were accepted. There seems to be no change in the number of applicants from

these schools, and in general, the local boards of membership found in their favor more often than they have done in the past. During the year only 130 graduates of approved schools applied, or 10 less than the number in the other two categories. Some of this falling off may be attributed to the claims of the armed forces on these men. However, the continued decrease, both in numbers and proportions, of graduates of Class A schools seeking membership in the Society is a source of real concern to the committee and merits serious study.

There is appended a list of medical schools approved by the committee.

ROBERT T. MONROE, *Chairman*

\* \* \*

##### LIST OF MEDICAL SCHOOLS AND COLLEGES APPROVED BY THE COMMITTEE ON MEDICAL EDUCATION OF THE MASSACHUSETTS MEDICAL SOCIETY

###### ARKANSAS

University of Arkansas School of Medicine, Little Rock.

###### CALIFORNIA

University of California Medical School, Berkeley, San Francisco.

College of Medical Evangelists, Loma Linda, Los Angeles.

University of Southern California School of Medicine, Los Angeles.

Stanford University School of Medicine, Stanford University, San Francisco.

###### COLORADO

University of Colorado School of Medicine, Denver.

###### CONNECTICUT

Yale University School of Medicine, New Haven.

###### DISTRICT OF COLUMBIA

Georgetown University School of Medicine, Washington.

George Washington University School of Medicine, Washington.

Howard University College of Medicine, Washington.

###### GEORGIA

Emory University School of Medicine, Atlanta.

University of Georgia School of Medicine, Augusta.

###### ILLINOIS

Loyola University School of Medicine, Chicago.

Northwestern University Medical School, Chicago.

Rush Medical College, University of Chicago, Chicago.

The School of Medicine of the Division of the Biological Sciences, University of Chicago, Chicago.

University of Illinois College of Medicine, Chicago.

###### INDIANA

Indiana University School of Medicine, Bloomington, Indianapolis.

###### IOWA

State University of Iowa College of Medicine, Iowa City.

###### KANSAS

University of Kansas School of Medicine, Lawrence, Kansas City.

###### KENTUCKY

University of Louisville School of Medicine, Louisville.

nesses of the districts and the military educational needs as they may affect the medical profession.

On May 12, 1942, the Executive Committee and Program Committee of the New England Postgraduate Assembly voted to postpone the assembly for the duration. This vote was almost unanimous among the New England state medical societies.

The committee announces that the Clinical Congress of the Connecticut State Medical Society will be held next September, further announcement of this event will be made in the *New England Journal of Medicine*.

At the present time the committee is studying the problems of postgraduate instruction in the field of industrial medicine, particularly as it relates to the defense industries. Announcement concerning this phase of postgraduate instruction will be made in the *New England Journal of Medicine* later in the summer.

REGINALD FITZ, *Chairman*  
LEROY E. PARKINS, *Secretary*

## APPENDIX NO 10

### REPORT OF THE COMMITTEE ON PHYSICAL THERAPY

It should be of interest to the members of the Council to realize that in Greater Boston we have four excellent schools for training physical therapy technicians which fulfill every requirement of the American Medical Association. We also have, however, several other schools operated largely from a commercial viewpoint, these provide the pupil with a training so superficial as to be utterly inadequate for a successful career. Cases have come to our attention where the high school teacher who is designated as 'vocational adviser' has probably entirely from ignorance of the situation suggested one of these schools to the inquiring high school senior because of its shorter course. These commercial schools have few or no clinical opportunities and are extremely limited in the quality of their instruction. Their courses are so short that they average but eight months or from three to five half-days each week, this is not one quarter the time required to grasp adequately the basic fundamentals necessary for the work of a physical therapy technician.

Many teachers acting as vocational advisers are too busy to investigate the various schools in the many types of work open to the graduating pupils. Consequently the easiest procedure is to hand out an advertising pamphlet that has been sent from these schools and with it comes to the pupil the implied recommendation of the adviser.

In an attempt to correct this situation your committee has been of practical help by disseminating information concerning the teaching of physical therapy to the Hospital Council of Boston, to occasional private inquirers, to the high school teachers and vocational advisers, and to the State Office of Secondary Education. An article pertaining to the selection of schools for the training of physical therapy technicians is to be printed in *Massachusetts Teacher*, a publication that reaches 27,000 teachers. A small but increasing number of requests are being received by your committee for advice and information pertaining to this phase of our work. This recent undertaking has already accomplished encouraging results.

There are probably a goodly number of counselors who are vitally interested in the schools of their cities. The committee urges that, in justice to our high-school graduates you lend your influence to this problem. This may be done by conferring with the adviser in your high school or by seeing that she gets in touch with the office

of the Massachusetts Medical Society or with this committee, for desired information concerning curriculum, clinical facilities and instruction of these various schools for training physical therapy technicians.

FRANKLIN P. LORRA, *Chairman*  
GEORGE R. MINOT  
ROBERT B. OSGOOD

## APPENDIX NO 11

### REPORT OF THE COMMITTEE TO CONSIDER EXPERT TESTIMONY

Your committee was appointed at the Springfield meeting of the Society in 1936 to consider certain matters included in the report of the Committee on Ethics and Discipline. Since the work of your committee is still incomplete, this must be a report of progress only.

Many difficulties in the work of the committee have been encountered. Many conferences have, however, been held between the chairman and other members. A long illness of the chairman in 1939 further delayed the work, but since the middle of 1940 much groundwork has been laid and considerable accomplished.

It was early appreciated by your committee that to function and accomplish the purpose of its being it would be desirable and necessary to have the help of the Massachusetts Bar Association as well as that of members of the General Court especially those members connected with legal affairs.

The president of the Massachusetts Bar Association from 1940 to 1941 was most co-operative. Unfortunately he left this office before he was able to appoint a committee from the Massachusetts Bar Association to work with our committee. The president of the Bar Association at the present time also is much interested and in December 1941 appointed the late Harold P. Small of Springfield, to serve as chairman of a committee and to select the other members of the committee. Unfortunately, Mr. Small died very suddenly on January 1, and in their delay has ensued.

Mr. Tschol Peterson, a member of the State Senate, has also been most helpful and will continue to be. Mr. Peterson in his many conferences with the chairman stressed the fact that the work of your committee is of necessity of considerable delicacy, that it should be carried out slowly and with the assistance of a committee from the Massachusetts Bar Association is mentioned earlier.

As matters stand at present your committee has been forced to hold in abeyance any further deliberations, subject to the appointment of a committee from the Massachusetts Bar Association or from some other legal society in the State.

GEORGE LEONARD SCHULT, *Chairman*  
DAVID CIEFFER  
JAMES J. GOODWIN  
HENRY C. MERRILL  
FRANCIS P. MCCARTHY

## APPENDIX NO 12

### REPORT OF COMMITTEE TO EQUALIZE DISTRIBUTION AMONG PHYSICIANS OF MEDICAL SERVICE TO WPA EMPLOYEES

As was expected the WPA roll has continued to decrease in numbers. Last month there were approximately 30,000 workmen and the lowest accident case record—

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTE-MORTEM AND POST-MORTEM RECORDS AS USED  
IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

### CASE 28261

#### PRESENTATION OF CASE

A forty-nine-year-old millworker was admitted to the hospital because of a disturbance of vision and occipital headaches.

For several years before entry, the patient had occasional difficulty in understanding things said to him. He attributed this to "poor hearing." Two years before entry, he began to have suboccipital and less often frontal or parietal headaches once or twice a week and, as a rule, lasting half a day. About a year before entry, the patient became aware of inability to see objects to the left of him. There was no disturbance of central vision. For about three months before entry, the headaches were accompanied by unsteadiness of gait; during the headaches, the patient staggered and tended to fall to the left. He became somewhat irritable, and seemed to be preoccupied with past events. Memory for recent events was impaired. He had to "stop and figure out" his previously habitual duties as a loom-tender in a mill. About this time, he began to regurgitate food and sour material immediately after swallowing. Once he vomited.

The family and past histories were irrelevant.

On admission, the patient appeared well developed and nourished, co-operative, fairly intelligent and well oriented. The heart, lungs and abdomen seemed normal. There was moderate scoliosis of the thoracic spine, with convexity to the right. There was partial left homonymous hemianopsia, the maculae being unaffected. The optic fundi were normal. The right pupil was slightly irregular and slightly smaller than the left; both reacted well to light and distance. Ocular movements were normal. There was no nystagmus. Tests of hearing showed questionable reduction in air conduction in the left ear. The gait was normal, with eyes open or closed. There were slight weakness and slightly increased muscular tone in the left arm. The reflexes were thought to be normal.

The temperature, pulse and respirations were normal. The blood pressure was not recorded.

Examinations of the blood and urine were negative. The blood Hinton reaction was negative. A lumbar puncture gave clear, colorless fluid under

an initial pressure of 280 mm. of mercury. There were 3 lymphocytes per cu. mm.; the total protein was 216 mg. per 100 cc., the gold-sol curve was 0011221000, and the Wassermann reaction was negative.

An electroencephalogram was suggestive of a lesion on the right side near the midline in the parietal region. Roentgenograms of the upper gastrointestinal tract and of the chest were negative.

A ventriculogram showed incomplete filling of the right lateral ventricle, with displacement of both ventricles toward the left. A Mixter punch introduced into the right temporal lobe to a depth of 5 cm. gave the operator a gritty sensation, but examination of the biopsy specimen was negative.

On the nineteenth hospital day, an operation was performed.

#### DIFFERENTIAL DIAGNOSIS

DR. WILDER PENFIELD\*: Was the patient right handed, or left handed?

DR. CHARLES S. KUBIK: He was right handed.

DR. PENFIELD: Is it permissible to see the x-ray films of the skull?

DR. TRACY B. MALLORY: You are welcome to see them at any moment you like.

DR. PENFIELD: Is there a calcification corresponding to the gritty sensations reported?

DR. AUBREY O. HAMPTON: Here are some plain films taken before the encephalogram. The only calcium I see appears to be in the pineal gland, and if this is the pineal gland it is displaced toward the right and the ventricles toward the left. That is very unusual.

DR. PENFIELD: If one takes the history and physical examination, the patient had a left homonymous hemianopsia, and it is said that there the maculae were not involved. So far as our clinical experience goes, that means that the interruption of the visual fields occurred posterior to the temporal region. On the other hand, one would like to know how carefully the maculae were investigated. The man had evidence of increased intracranial pressure, and one assumes that he had a cerebral tumor. The encephalogram showed displacement from the right to the left, but it seems to me that this calcification is too low and too far anterior to be a pineal body, and one sees in the anteroposterior view calcification at this point that might correspond with that on the right side.

For a snap diagnosis, I should be driven to the conclusion that this man had an expanding lesion, that the calcification probably lay in the expanding

\*Director, Montreal Neurological Institute, McGill University Faculty of Medicine; professor of neurosurgery, McGill University Faculty of Medicine, Montreal.

lesion, and that the expanding lesion was in the right posterior temporal region.

A PHYSICIAN: Temporal?

DR. PENFIELD: Temporal, because of the x-ray findings, which I am accepting. I assume that Dr. Hampton takes that as the proper position for the pineal gland, and that the calcification in the anteroposterior view is on the right side.

DR. HAMPTON: It is on the wrong side for the ventricular displacement.

DR. PENFIELD: Then, may we not assume that this lies in the expanding lesion itself and corresponds with the gritty material that the operator encountered—indicating calcification in the x-ray film in the posterior temporal region?

DR. HAMPTON: It is very small. I do not know. It would be very fortunate if they tapped it.

DR. PENFIELD: At all events, clinically the patient had a lesion that should have been very near the calcified object, and this localization probably gave him homonymous hemianopsia. We have run into a group, about half a dozen, of small calcified neoplasms that occurred in the temporal region, usually deep in the temporal lobe—I am not sure that one or two did not lie on the other side of the inferior horn—and were of a type of neoplasm that is hard to define histologically. We called them—one or two of them, at any rate—hemangioblastomas or hemangiomas of some type. They were not gliomas. They did have vessels in them. We treated one or two by x-ray for long periods. I am thinking of a patient treated by Dr. Charles A. Elsberg. The x-ray picture was similar to that in the case under discussion, although there was a little more calcification. We operated, and there was an area of atrophy and evidence of both atrophy and some expansion.

Do you want me to "stick my neck out"?

DR. MALLORY: That is the custom.

DR. PENFIELD: Then, in spite of the report of the hemianopsia, with the unaffected maculae, which would make it occipital, I assume that this man had a neoplasm in the posterior temporal area, and that it might have been one of those tumors that are made up of many blood vessels that I do not know how to classify histologically.

DR. MALLORY: Would anyone like to ask Dr. Penfield any questions or suggest any alternative diagnoses?

A PHYSICIAN: What is your objection to meningioma?

DR. PENFIELD: A meningioma arising from the lesser wing of the sphenoid would have to be considered, but in our clinic meningioma is very rarely calcified, and if my assumption that this is neoplasm is correct, I should not consider a meningioma.

A PHYSICIAN: Would the total protein in the spinal fluid give you any inkling of the type of tumor?

DR. PENFIELD: I suppose that it suggests proximity of the tumor to the ventricle. I do not believe it indicates the nature of the tumor as a rule, although it might be that this was a neoplasm attached to the choroid plexus, with calcification in it.

A PHYSICIAN: There was considerable ataxia. How do you explain that?

DR. PENFIELD: I should explain it on the basis that the tumor might well have extended into the basal ganglion in some way. The patient had a pyramidal lesion involving the left side slightly. He had no true ataxia in the upper extremities with the eyes opened or closed.

DR. SAMUEL LEWIS: I have no additional information beyond what is available in the abstract.

In retrospect, it is my impression that the gritty sensation was not encountered when the needle was directed toward the temporal lobe. As I remember it, the gritty sensation was encountered when the right needle was directed in the usual position toward the posterior horn of the ventricle; no air was introduced into the right needle, but only into the left ventricle. The picture was satisfactory at that point, and there was no need for further study. There was no question that the gritty sensation was present, even though the biopsy at the time of the ventriculogram was negative, as was later brought out at the operation, when the same material was encountered. The position was not specifically temporal but perhaps seemed to be nearer the midline, and higher—parieto-occipital—according to the actual localization of the findings at operation.

DR. MALLORY: Will you continue and describe your findings at the craniotomy?

DR. LEWIS: I shall read the operative note:

Under intratracheal ether anesthesia, a medium sized temporo-occipital skin flap was turned down to within 2 cm of the midline, with a correspondingly large bone flap under the same area. The dura was incised with the pedicle at the top, toward the front. The cortex appeared normal, but felt soft over the posterior area of the exposure. Probing was done here, and the tumor encountered at a depth of about 4 cm. At this point of the procedure, Dr. John S. Hodgson entered the operation and opened the cortex down to the tumor and took a biopsy. There was no bleeding. (It was accepted at this time that the tumor was a meningioma.) The dura was closed along the anterior margin, the posterior margin of the cortex being left uncovered. Then, while the posterior margin of the scalp flap was retracted, the bone was undercut as far as possible, both from that point and from the bone flap where it was to be apposed—an extensive bone defect being left immediately over the tumor. The dura also had a defect here.

The undercut bone area was drained, as was the incision in the temporal muscle, and the wound was closed in two layers with silk. The patient was given two transfusions. Our plan in doing the operation in this way was to allow the ventricular system to displace the tumor nearer to the cortex at the point where cerebral hernia is certain to occur. At a second stage in six to eight weeks, we shall re-elevate this area of scalp and expect to effect an easier removal of the tumor.

The intention was to allow the tumor to migrate more toward the surface for a second-stage removal.

#### CLINICAL DIAGNOSIS

Parieto-occipital meningioma.

#### DR. PENFIELD'S DIAGNOSIS

Brain tumor (?), hemangioblastoma, posterior temporal region.

#### ANATOMICAL DIAGNOSES

Tuberculous meningitis.

Tuberculoma, posterior parietal region.

#### PATHOLOGICAL DISCUSSION

DR. MALLORY: The first attempt at a punch biopsy provided nothing from which a diagnosis could be made, but at the time of the craniotomy a second biopsy showed the characteristic wall of a tuberculoma, I think considerably to everybody's surprise. The patient then did very well for a long period, and it was three years before he began to develop serious symptoms of a different nature. He came in on the last occasion with a frank meningitis, and died in a comparatively brief period so that we have the findings of the autopsy, which will give us a little better check on the location of the lesion.

Dr. Kubik, will you tell us what the autopsy showed?

DR. KUBIK: There was a tuberculous meningitis. In the right posterior parietal and occipital region, above and lateral to the posterior horn of the ventricle, was a tuberculoma, from 2 to 3 cm. in diameter. This consisted of caseous material surrounded by a dense, fibrous capsule. Near it was a similar, smaller tuberculoma.

DR. MALLORY: Are there any other questions?

DR. PAUL BUCY: I should like to ask Dr. Lewis whether or not, when they found that this was a tuberculoma and in this location, an amputation of the occipital lobe might not have been considered.

DR. LEWIS: A second operation was considered, but the more conservative point of view prevailed. The patient made a surprisingly uneventful recovery. He was watched from the point of view of curiosity rather than from that of doing more about it.

DR. KUBIK: In another patient, operated on in 1931, there was a mass, the size of a small hen's

egg, in the parietal region. This differed from case under discussion in that the lesion was not and contained numerous small caseous foci. patient is still alive, eleven years later.

A PHYSICIAN: Was there any tuberculous elsewhere in the body?

DR. MALLORY: At autopsy, no active tubercles were found outside the central nervous system. Even the lungs were entirely normal.

A PHYSICIAN: How do you explain the nature of the lesion?

DR. MALLORY: I have little doubt that there was originally a pulmonary tuberculous infection, think, if the lungs had been examined with a more technic for Ghon's tubercle, we should have found it.

A PHYSICIAN: Were no tubercle bacilli found?

DR. MALLORY: Yes; they were found in spinal fluid on the last admission.

#### CASE 28262

#### PRESENTATION OF CASE\*

An eight-year-old boy was admitted to the hospital because of sudden progressive "fatness."

The patient was essentially well until three weeks before entry, when he was said to have "fallen into a river" and to have wet his legs. Two weeks before admission, he claimed to have had a "hard head cold," and at approximately the same time his family noted that he was "getting fat." The exact sequence of events was not entirely clear. The "fatness" was steadily progressive in severity, and during the week prior to entry his appetite became poor and he vomited three times but presented no other signs or symptoms of disease, either constitutional or referable to any of his symptoms. On the day before entry, his family physician examined the urine and advised admission to the hospital.

The patient had had the usual childhood diseases, and in addition had had a mastoiditis and a right mastoidectomy and a depressed skull fracture without unconsciousness, six months before entry. He had not had diphtheria or scarlet fever.

The family history was irrelevant.

Physical examination on admission revealed a pale, markedly edematous boy in no acute distress. The skin was dry, with keratinizing plugs in many of the hair follicles and desquamating scaly regions over the back. A small depressed area could be palpated in the left parietal bone. The eyes, including the fundi, were normal. A right mastoidectomy scar and some thickening and retraction of the left eardrum were noted. There was puffing

\*This case is presented through the courtesy of the Children's Hospital, Boston.

the face and eyelids, and the breath was urinous. Minimal dullness and diminution of breath sounds were noted at both lung bases. Otherwise, the lung fields were clear. The heart was described as possibly enlarged slightly to the left. An apical systolic murmur was present, which one observer described as soft and blowing, and another as loud and rough, accompanied by a thrill and transmitted to the base and left axilla. The second observer also described a split mitral second sound. The abdomen was slightly distended, but there were no palpable masses or organs, and no shifting dullness or fluid wave could be made out. The genitalia, extremities and sacral regions were edematous.

The temperature was 98°F., the pulse 88, and the respirations 20. The blood pressure was 135 systolic, 110 diastolic.

Examination of the blood showed a red-cell count of 2,500,000 with 65 per cent hemoglobin, and a white-cell count of 6800 with a normal differential. The urine was cloudy yellow and acid, with a specific gravity of 1.010 and a trace of albumin. It contained 0 to 5 red cells, 0 to 15 white cells, and 1 to 20 granular casts per high-power field. A blood Hinton reaction was negative, as was a tuberculin reaction in a dilution of 1:1000. The serum protein was 3.7 gm. and the nonprotein nitrogen 101 mg. per 100 cc. A throat culture grew out a few colonies of beta hemolytic streptococci and a moderate number of colonies each of pneumococci, *Haemophilus influenzae* and yellow staphylococci.

A roentgenogram of the chest showed enlargement of the heart both to the right and to the left, the total cardiac diameter being 12.1 cm., compared to a total internal diameter of the chest of 20.1 cm. There were also moderate pulmonary congestion and small bilateral pleural effusions. Films of the paranasal sinuses showed moderate irregular thickening of the mucous membranes lining the ethmoid and maxillar sinuses.

The patient was treated with magnesium sulfate orally and parenterally, transfused, and placed on limited fluids and a low-salt, high-protein diet. This resulted in improvement of the edema, but the blood pressure remained about 140 systolic, 100 diastolic. The urine continued to show red cells, white cells, abundant granular and cellular casts, and a trace to a large trace of albumin. A urea-clearance test on the third hospital day showed 6 per cent of normal function. On the sixth hospital day, the nonprotein nitrogen was 133 mg. per 100 cc. On the eighth day, the patient complained of severe sore throat and some cough. He was nauseated and somewhat orthopneic. The temperature was 100°F., and the pulse rapid and weak,

with a pulse deficit. The blood pressure rose to 170 systolic, 120 diastolic. The heart action was rapid, with poor sounds and a gallop rhythm. There was enlargement of the liver, and rales were present over both lung bases. An electrocardiogram showed slight left-axis deviation and suppression of T<sub>2</sub>. The patient was treated with morphine, and rapid digitalization was attempted; however, the pulmonary edema increased in severity, and the pulse became irregular and thready. An electrocardiogram showed a slight prolongation of the PR interval. Terminally, Cheyne-Stokes respirations developed. The patient died on the ninth hospital day, approximately three weeks after the onset of his illness.

#### DIFFERENTIAL DIAGNOSIS

DR. ALLAN M. BUTLER: I should like to remark on a few points in the description of this case. "The skin was dry, with keratinizing plugs in many of the hair follicles and desquamating scaly regions over the back." Such findings are present with a vitamin A or C deficiency but hardly ever in an essentially healthy boy of eight years of age. One can have scaly desquamation, perhaps, following scarlet fever.

"The abdomen was slightly distended, but there were no palpable masses or organs, and no shifting dullness or fluid wave could be made out." One wonders whether the edema masked a slightly enlarged liver. On the other hand one could have these signs of cardiac failure in a patient with acute nephritis without much in the way of enlargement of the liver, since the failure is usually left sided.

"A roentgenogram of the chest showed enlargement of the heart both to the right and to the left." Such cardiac enlargement is common in acute hemorrhagic nephritis.

"There were also moderate pulmonary congestion and small bilateral pleural effusions"—I suppose because of congestive failure.

"An electrocardiogram showed slight left-axis deviation and suppression of T<sub>2</sub>." In other words, there was some myocardial involvement.

Much of this history is typical of the history of an acute initial hemorrhagic nephritis. The patient had an upper respiratory infection two weeks preceding the onset of the present illness. The gain in weight, of course, was due to edema. He had anorexia and vomiting, and the urine contained albumin, red cells and casts. He had hypertension and the signs of myocardial failure. On the other hand, certain facts and lack of information in the history make one wonder whether the autopsy will reveal either some evidence of an antecedent cardiac lesion, a previous nephritis,

which was latent before the present exacerbation, a congenital anomaly, which resulted in diminished renal function, or a previous pyelonephritis, which likewise caused diminished renal reserve. The lack of information pertains to the statement that the patient was essentially well. One wonders whether he was fairly well or really a robust, healthy boy of eight. Then we find that he entered the hospital two weeks after an upper respiratory infection, with pallor and marked edema. Usually, a patient with acute initial hemorrhagic nephritis does not have marked pallor and is not markedly edematous. On the other hand, it is possible to have an acute hemorrhagic nephritis that is accompanied by marked degenerative changes throughout the entire parenchyma of the kidney. Edema then appears very rapidly, and may become as extensive as that seen in nephrosis. Moreover, the patient had a uriniferous breath, which is very rare in acute initial hemorrhagic nephritis.

I should pass over the question of the murmur in the heart as being no evidence of endocarditis or congenital heart disease and say that it was a systolic murmur due to dilatation of the heart such as is observed so frequently in acute hemorrhagic nephritis. The red-cell count of 2,500,000 and the hemoglobin of 65 per cent confirm the pallor and are rather unusual in acute initial hemorrhagic nephritis unless accompanied by very extensive degenerative changes throughout the tubules and general parenchyma of the kidneys—in other words, a very severe fulminating type of hemorrhagic nephritis, which is unusual in children. Next, we notice a specific gravity of 1.010, which in a boy with acute initial hemorrhagic nephritis in the stage of edema is very rare because such patients almost always have oliguria, and the urine concentration is almost always quite good. Oliguria and good specific gravity of the urine are characteristic of initial hemorrhagic nephritis, and this boy seems to have had neither.

In considering the urine sediment, I should like to know whether it was centrifuged, because I know that at the Children's Hospital half the people examine uncentrifuged and half centrifuged sediments and the records rarely show which was done—0 to 5 red cells if uncentrifuged are a lot; if centrifuged, they are not. There were 1 to 15 white cells. White cells predominate over the red cells; this suggests what Addis and Oliver\* call a "degenerative element." Granular casts and epithelial cells are not mentioned.

DR. TRACY B. MALLORY: The report on one centrifuged specimen says that there were 15 to 30 red blood cells and 3 to 5 white blood cells per

high-power field; it was also reported to "loaded" with granular casts and some white blood cell casts, but there is no mention of epithelial cells.

DR. BUTLER: Usually, with a marked element of degenerative changes, there are epithelial cells in the urinary sediment. No mention is made of a urine culture, and sometimes one is surprised to find that there is infection along with what appears to be uncomplicated acute hemorrhagic nephritis.

The serum protein was 3.7 gm. per 100 cc. In the ordinary case of acute initial hemorrhagic nephritis, the serum protein may come down, but usually not to 3.7 gm. in two weeks. If it does, there is usually a marked involvement of the entire kidney. We have such a boy on the ward at the present time, with a serum protein around 3 gm. whose hemorrhagic nephritis from the history appears of apparently short duration, and he puzzled me for that reason.

The nonprotein nitrogen was 101 mg. per 100 cc. That is very high for a patient with initial acute hemorrhagic nephritis and a urine with a specific gravity of 1.010. Usually, such a specific gravity and urine volume suggest that the oliguric stage has been passed, and the nonprotein nitrogen would be on the way down and not high as 100 mg. Certainly, it is too high for a patient with nephrosis.

On the third hospital day,—that is, a week more after the onset of the anorexia and nausea and the finding of abnormal urine sediment by the family physician,—the urea clearance was 10 per cent, and that again is very unusual in a patient with simple initial hemorrhagic nephritis and again indicates to me that there was either some abnormality in the kidney existing at the onset of this acute hemorrhagic nephritis or very extensive nephritis extending far beyond the glomerular involvement of an ordinary hemorrhagic nephritis. On the sixth day, the nonprotein nitrogen was 133 mg.—still going up.

In summary, I should think that this patient had an acute hemorrhagic nephritis, the cause of death being myocardial failure. Autopsy will show a dilated heart; I do not know whether it will be very hypertrophied or not. Usually, in patients who die of myocardial failure during an acute hemorrhagic nephritis, the pathologists find relatively little at examination. This suggests that the myocardial failure is due to a vascular disturbance within the myocardium, similar to that affecting most of the other organs of the body in acute hemorrhagic nephritis. I do not know whether we shall find that this was one of the very diffuse, rapidly progressing types of acute

\*Addis, T., and Oliver, J. *The Renal Lesion in Bright's Disease*. 628 pp. New York: Paul B. Hoeber, Inc., 1931.

initial glomerular nephritis with degenerative changes involving all the parenchyma of the kidney as well as the glomeruli, or whether we shall find that there existed a congenital anomaly, an old renal infection with scarring, or an unnoticed nephritis previous to this acute hemorrhagic nephritis. I believe that the kidneys were large and edematous. With the anemia and with low serum protein, I think that they perhaps were not so red as the usual red swollen kidneys of glomerulonephritis.

#### CLINICAL DIAGNOSES

Acute hemorrhagic nephritis  
Terminal heart failure

#### DR. BUTLER'S DIAGNOSES

Hemorrhagic nephritis  
Cardiac dilatation  
Hypertension  
Myocardial failure, with congestion characteristic of right-sided and left-sided cardiac failure  
Either pre-existing congenital anomaly or infection of urinary tract, pre-existing nephritis or superimposed degenerative changes involving all elements of renal parenchyma

#### ANATOMICAL DIAGNOSES

Acute and chronic glomerulonephritis, with degenerative vascular lesions in kidneys, terminal  
Anasarca  
Cardiac hypertrophy, with terminal congestive failure  
Congenital incomplete defect of interventricular septum  
Tracheobronchitis and bronchopneumonia

#### PATHOLOGICAL DISCUSSION

DR. SIDNEY FARBER\* The clinical diagnoses were acute hemorrhagic nephritis and terminal cardiac failure. At post mortem examination, we found massive edema of the periphery, fairly well marked ascites, marked pleural effusion

and pericardial effusion. There was terminal congestive failure, with pulmonary edema and marked congestion of the liver and the abdominal viscera. The kidneys were somewhat enlarged, — about 25 per cent above weight, — red and rather congested. Some of the redness disappeared after standing. The parenchyma was more yellow than appeared at first glance. There was a diffuse glomerulonephritis perfectly consistent with what one would expect from the history. There were two other findings, glomerular lesions that must have gone back at least a year and were diffuse and not too numerous, but were easily found throughout both kidneys, and the blood vessels showed fibrin degeneration of the walls, particularly in the afferent arterioles, and in the glomerular loops.

The heart was almost twice the normal weight, and there was, as Dr. Butler indicated, very little evidence of cardiac inflammation. There was some fatty degeneration of the myocardium as is sometimes found in cases of this kind, and a good deal of edema of the myocardium. I neglected to mention that, in addition to the pulmonary edema and congestion, there was a very important tracheobronchitis, with destructive lesions in the bronchioles.

The brain was considerably increased in weight, with a definite pressure cone at the base. The heart showed, in addition to the findings already described, a congenital malformation. It is the first of its kind that I have had the opportunity to see. Here, at the base of the aortic valve in the region of the undefended space where the interventricular septal defect is so often found, was an incomplete defect of the septum with no actual communication between the left and right sides of the heart. We have an adequate basis for a murmur, then, if one was actually heard.

In summary, this was a case of acute glomerulonephritis, with evidence of older glomerulonephritis that must have gone back at least a year. In the kidneys, there was also evidence of acute degenerative lesions in the arterioles and glomerular capillaries, which, for want of a better explanation, I should associate with the hypertension. The other findings were secondary to the kidney disease.

\*Assistant professor of pathology, Harvard Medical School, Boston, Mass.



# The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established in 1828

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND  
PUBLISHED UNDER THE JURISDICTION OF THE  
COMMITTEE ON PUBLICATIONS

Official Organ of  
THE MASSACHUSETTS MEDICAL SOCIETY  
and  
THE NEW HAMPSHIRE MEDICAL SOCIETY

## EDITORIAL BOARD

Joseph Garland, M.D.	Stephen Rushmore, M.D.
William B. Breed, M.D.	Henry R. Viets, M.D.
George R. Minot, M.D.	Robert M. Green, M.D.
Frank H. Lahey, M.D.	Charles C. Lund, M.D.
Shields Warren, M.D.	John F. Fulton, M.D.
George L. Tobey, Jr., M.D.	A. Warren Stearns, M.D.
C. Guy Lane, M.D.	Dwight O'Hara, M.D.
William A. Rogers, M.D.	Chester S. Keefer, M.D.

## ASSOCIATE EDITORS

Thomas H. Lanman, M.D.	Donald Munro, M.D.
Henry Jackson, Jr., M.D.	

Walter P. Bowers, M.D., EDITOR EMERITUS  
Robert N. Nye, M.D., MANAGING EDITOR  
Clara D. Davies, ASSISTANT EDITOR

**SUBSCRIPTION TERMS:** \$6.00 per year in advance, postage paid, for the United States (medical students, \$3.50 per year); Canada, \$7.04 per year, Boston funds; \$8.52 per year for all foreign countries belonging to the Postal Union.

**MATERIAL** for early publication should be received not later than noon on Friday.

**THE JOURNAL** does not hold itself responsible for statements made by any contributor.

**COMMUNICATIONS** should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston, Massachusetts.

## MATERNAL MORTALITY

TEN years ago, the appallingly high maternal mortality in the United States was a national disgrace, and there were insistent demands from both the laity and the medical profession that something be done about it. Now it begins to look as if something had been accomplished. In 1939, the United States had a maternal mortality of 4.0 per 1000 live births—the lowest recorded in this country; in 1930, the rate was 6.7. In 1933, the rate in Massachusetts was 6.7, and it has dropped every year but one since then, to a level of 2.8 in 1940.

Many factors have combined to produce this lowering of maternal mortality. Doubtless, one of the most important has been the extension and

improvement of state and local public services for maternal health, made possible by the provisions of the Social Security Act. The American Committee on Maternal Welfare, Incorporated, with its component organizations, and the state and local maternal-welfare committees have done extremely valuable work.

One of the best examples of what a local committee can accomplish is furnished by the recently published report of the Committee on Maternal Welfare of the Philadelphia County Medical Society.\* For ten years, this committee has worked with patience and intelligence to educate physicians, hospital administrators and the laity. It began with a critical study of maternal death and subsequently extended the study to include stillbirths and neonatal deaths. It early perceived the need for supervision of the work of courtesy staff members and secured the adoption by most hospitals of uniform regulations governing such work. It formulated and adopted a standard governing the admission of toxic patients for hospital treatment. It has induced nearly half the hospitals to provide class instruction in the essentials of good prenatal care and has even provided series of talks for prospective fathers. It has a subcommittee working on the problem of securing uniformity in obstetric hospital records and in reports of obstetric results. Most significant of all perhaps, it has induced nearly all the Philadelphia hospitals with maternity departments to hold regular staff conferences, to which courtesy members are invited, for the open discussion of maternal deaths, stillbirths and neonatal deaths. All this has resulted in a lowering of the maternal mortality rate in Philadelphia from 7.3 and 7.5 per 1000 live births in 1931 and 1932, respectively, to 2.4 in 1940.

It is instructive to calculate the diminution in the total number of deaths that results in this lowering of the mortality rate. From 1932 to 1940, inclusive, there were 1263 obstetric deaths in Philadelphia. Had the maternal mortality rate

\*Maternal mortality: Philadelphia, 1931-1940. Report of the Committee on Maternal Welfare, Philadelphia County Medical Society. *Weekly Report and Medical Digest* (November 22, 1941).

remained at the 1932 level, 7.5, the total deaths in the ensuing nine years would have been 2037. This is a significant and gratifying drop in maternal mortality, and the Committee on Maternal Welfare in Philadelphia deserves a large share of the credit for it.

### CASEY WOOD (1856—1942) AND AMERICAN MEDICINE

THE death of Casey A. Wood, in California, January 26, 1942, brings to an end one of the most remarkable and indeed unique careers in American medicine. Trained on the Continent and in England as an ophthalmologist, Wood became one of the best known students of diseases of the eye in this country. From 1890, when he first went to Chicago to practice, until he retired in 1917, his name was probably more familiar to both ophthalmologists and physicians in general than that of any other man in his special field. He wrote books; edited systems and encyclopedias, served as editor of three successive journals between 1894 and 1914, the *Annals of Ophthalmology*, the *Ophthalmic Record* and the *American Journal of Ophthalmology*; and corresponded with practically every prominent man in his branch of medicine both in this country and abroad.

Wood began his life in Wellington, Ontario, Canada, November 21, 1856, the son of American parents. After an early training in English and French schools in Canada, he went to Bishop's College in Montreal where he received his M.D. in 1877. McGill University also granted him an M.D. in 1906 and made him LL.D. in 1921. Wood became a student at the New York Eye and Ear Infirmary in 1886 and then spent a number of years at the University of Berlin and in various London hospitals, "Moorfield," Middlesex and others. When he settled in Chicago in 1890 (his first book was published in Detroit in 1891), he was one of the best trained men in his profession in America. He soon rose to teaching positions to the professorship of ophthalmology in both Northwestern University and the University of

Illinois. From 1917 to 1919, he served in the Medical Corps of the U. S. Army, ending his service on the staff of the Surgeon General in Washington as a Lt. Colonel, M.C., and was retired with the rank of Colonel in the Medical Reserve.

The historical side of medicine always interested Casey Wood. He began to collect books even before his Chicago days, became associated with Dr. Mortimer Frank, Dr. Arnold C. Klebs and other historically minded physicians and, in 1902, exhibited at the annual meeting of the American Medical Association examples of British and American ophthalmic literature, with the aid of Dr. Harry Friedenwald, of Baltimore, Dr. A. A. Hubbell, of Buffalo, and Dr. A. R. Baker, of Cleveland. The four men had enough books, privately owned, to make the unusual exhibit possible, and Wood wrote up the story in the November 8 and 15, 1902, issues of the *Journal of the American Medical Association*. From then on, hardly a day passed without some progress in his study of the history of ophthalmology. Numerous trips to Europe, three years in India and Ceylon and many trips to the West Indies served his purpose, and especially during the last few years, he was a constant seeker of manuscripts in European libraries, having digested all the printed books he could find on the subject. Making his headquarters in Rome, he sent out scouts in all directions, copying, photographing or collecting the intricate medieval handwritten material in Latin, Hebrew, Arabic and Greek. It was an exacting task, requiring a skilled mind, but Wood made himself as much at home in this scholarly field as he had in ophthalmology itself.

The present war dealt him a severe blow. When the writer of this note saw him in August, 1939, in Geneva, the forewarnings of conflict had already closed many libraries to him, and a distracted man looked out on a crumbling world. He was not immediately beaten, however, for he escaped to America to live in his native country, of which he was so fond, for the last two years of his life.

His most important historical work was the translation of *De Oculis* (Stanford University, 1929), by

Benevenutus Grassus, and he will long be remembered for his charming selection, with Dr. F. H. Garrison, of the poems in *A Physician's Anthology* (London, 1920).

Wood was also somewhat of a zoologist, and in his travels in India and Ceylon, and in British Guiana with William Beebe, he studied the ophthalmology of birds. When about sixty, he published his important book, *Fundus Oculi of Birds* (Chicago, 1917). After many years of labor, he compiled and edited *An Introduction to the Literature of Vertebrate Zoology* (London, 1931), based on the books in the various libraries at McGill University. A library, devoted to ornithology, he gave to McGill in honor of his wife.

Thus passes an American physician, a distinguished scholar, a friend to Canada and a man whose influence, widely felt in his time, will continue in the inspiration he gave so generously to others.

## MEDICAL EPONYM

### VON PIRQUET REACTION

Clemens F. von Pirquet (1874-1929) described "Tuberkulindiagnose durch cutane Impfung [Tuberculin Diagnosis by Means of Cutaneous Inoculation]" before the Berlin Medical Society on May 8, 1907, and his remarks were reported in the *Berliner klinische Wochenschrift* (44:644, 1907). A portion of the translation follows:

If a tuberculous child is inoculated with tuberculin, there appears at the site of the inoculation a small papule that is bright red at first, gradually becomes dark red, and fades out within a week. . . . Nearly all cases of clinical tuberculosis in children give a positive reaction. . . . With increasing age, the reaction becomes more and more frequent, so that among adults nearly all patients show this reaction.

R. W. B.

## MASSACHUSETTS MEDICAL SOCIETY

### COMMITTEE ON MATERNAL WELFARE

#### CASE HISTORY: ACUTE INVERSION OF THE UTERUS RESULTING IN FATAL HEMORRHAGE

A thirty-year-old woman in her second pregnancy, which had been entirely uncomplicated and adequately supervised, was delivered at term by breech extraction of a living child. The past

history was irrelevant: the first pregnancy was normal, and there had been no serious illnesses or surgical operations. Following the birth of the baby, the placenta did not separate immediately, and Credé's method was resorted to; the uterus became inverted. The bleeding from this inversion was tremendous, and attempts to reinvert the uterus were unsuccessful. A tourniquet was placed about the inverted portion to control hemorrhage, but in spite of this and a transfusion of 750 cc. of whole blood, the patient died from hemorrhage and shock.

*Comment.* Such deaths must be considered avoidable. When a uterus inverts during attempt to deliver the placenta by fundal pressure, it is natural to suppose that the manipulation is the cause of inversion; certainly, such inversion is not spontaneous. This patient was under the care of a general practitioner, who sought the assistance of a surgeon when the inversion occurred. The bleeding was tremendous, and by the time the consultant arrived the internal os had so shut down on the inverted fundus that replacement under an anesthetic could not readily be accomplished. Practically every inverted uterus can be immediately replaced with a patient under full anesthesia and when it is so replaced, packing of the uterus to stimulate contraction and control further bleeding is indicated. Manipulation cannot effect replacement in some cases, and laparotomy is indicated. The use of a tourniquet to control hemorrhage in a case of inversion is evidence of failure.

It has been noted in these columns that chronic inversion of the uterus occasionally results from an acute inversion, and there is at least one case in which a uterus has been chronically inverted for several months and after replacement has functioned normally, with delivery of a full-term child.

All patients who bleed should, of course, be transfused, and the transfusion should be given before the patient is in extremis.

### DEATHS

EATON — CHARLES A. EATON, M.D., formerly of Boston, died recently. He was in his sixty-fifth year.

Born in Winchester, New Hampshire, Dr. Eaton received his degree from Boston University School of Medicine in 1908. He was a former member of the Massachusetts Medical Society and the American Medical Association.

His widow and two sisters survive him.

McGUINNESS — JOHN F. McGUINNESS, M.D., of Woburn, died June 17. He was in his fiftieth year.

Born in Brighton, Dr. McGuinness received his degree from Middlesex University School of Medicine in 1922. He was a member of the Massachusetts Medical Society and the American Medical Association.

His widow and two daughters survive him.

## WAR ACTIVITIES

## CIVILIAN DEFENSE

## NEW APPOINTMENTS

New appointments for two members of the Executive Committee of the Medical Division, Massachusetts Committee on Public Safety, have recently been announced.

Dr A William Reggio, deputy medical director of the Medical Division, has been commissioned as a major in the United States Public Health Service and will devote the majority of his time to perfecting the organization of the Medical Division for the care of injured civilians in the Commonwealth.

Mr Oliver G Pratt, superintendent of the Salem Hospital and also a deputy medical director of the Medical Division, has been made a consultant in the United States Public Health Service and has been appointed State Hospital Officer, whose duties comprise the organization of hospitals for civilian defense activities. These include blood banks, the establishment of emergency and big hospitals and an accounting to the Government for the cost of hospitalization of civilian casualties. A ruling having been recently made in Washington that civilians injured by bombing or sabotage or during an official blackout may receive federal assistance for hospital care at the rate of \$375 a day.

## MISCELLANY

RESUME OF COMMUNICABLE DISEASES  
IN MASSACHUSETTS FOR MAY 1942

DISEASES	MAY 1942	MAY 1941	FIVE YEAR AVERAGE*
Anterior poliomyelitis	2	0	0
Chicken pox	17	17	1187
Diphtheria	18	9	34
Dog bite	1387	1359	12.4
Dysentery bacillary	5	7	234
German measles	2440	740	368
Gonorrhea	321	319	34.9
Measles	5326	4118	10
Meningitis meningococcal	20	8	79
Meningitis other forms	10	—	—
Mumps	2018	14.9	965
Paratyphoid infections	3	23	372
Pneumonia lobar	211	210	545
Scarlet fever	1128	873	491
Syphilis	573	437	267
Tuberculosis pulmonary	362	303	25
Tuberculosis other forms	23	30	6
Typhoid fever	1	12	5
Undulant fever	971	1157	649
Whooping cough			

\*Based on figures for preceding five years

## GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Anterior poliomyelitis was reported from Chelsea, 1, Lowell, 1, total, 2.  
Diphtheria was reported from Boston, 1, Canton, 2, Fall River, 4, Hampden, 2, Lowell, 1, Millbury, 1, Somerville, 3, Springfield, 2, Winthrop, 1, Wrentham, 1, total, 18.  
Dysentery, bacillary, was reported from Boston, 1, Melrose, 1, Waltham, 3, total, 5.  
Encephalitis, infectious, was reported from Bridgewater, 1, Cambridge, 1, Fort Devens, 1, Quincy, 1, total, 4.  
Meningitis, meningococcal, was reported from Agawam, 1, Boston, 5, Carver, 1, Chelsea, 2, Leominster, 4, Lynn, 2, Newton, 1, Salem, 1, Townsend, 1, Uxbridge, 1, Weymouth, 1, total, 20.  
Meningitis, other forms, was reported from Boston, 1, Cambridge, 1, Chicopee, 1, total, 3.

Nauck, 1, Peabody, 1, Salem, 1, Somerville, 1, Springfield, 1, total, 10.

Paratyphoid infections were reported from Melrose, 1, Quincy, 2, total, 3.

Sepic sore throat was reported from Amesbury, 1, Arlington, 1, Barre, 2, Belmont, 1, Boston, 2, Brookline, 2, Cambridge, 1, Medford, 3, Winchester, 1, Winthrop, 2, total, 16.

Tetanus was reported from East Brookfield, 1, Nauck, 1, Newton, 1, total, 3.

Trichoma was reported from Quincy, 1, total, 1.

Trichinosis was reported from Amherst, 1, Canis, Edwards, 1, Trunton, 1, total, 3.

Typhoid fever was reported from Fitchburg, 1, Randolph, 1, total, 2.

Undulant fever was reported from Waltham, 1, total, 1.

Chicken pox for the second consecutive month reached figures of record high incidence. Mumps again is at a record high level for the ninth month of the past ten months.

Reported at figures above their five year average incidences were anterior poliomyelitis, chicken pox, diphtheria, dog bite, German measles, measles meningococcal meningitis scarlet fever, syphilis, pulmonary tuberculosis and whooping cough.

Bacillary dysentery, gonorrhea, paratyphoid infections, lobar pneumonia, tuberculosis, other forms, typhoid and undulant fever were all reported at figures below their five year averages.

One case of animal rabies was reported from Norwell, possibly the start of a new focus in this area.

## NOTES

Tufts College Medical School recently announced the following promotions on the faculty. Dr James M. Baty, professor of pediatrics, Dr Francis C. McDonald, clinical professor of pediatrics, Dr Richard Wagner, assistant professor of pediatrics, Dr Bernard Appel, assistant professor of dermatology, Dr Francis P. McCarthy, lecturer in dermatology, and Dr Harry M. Powers, associate professor of biochemistry.

Dr Elmer W. Barron has been made professor emeritus of pediatrics. He has been head of that department since 1929 and has taught at the medical school since 1910.

Dr Philip D. Woodbridge, a former member of the staffs of the Lahey Clinic and Boston Consumptives and Boston City hospitals, was recently appointed professor of anesthesiology at Temple University School of Medicine, Philadelphia.

## REPORTS OF MEETINGS

## GREATER BOSTON MEDICAL SOCIETY

A regular meeting of the Greater Boston Medical Society was held at the Beth Israel Hospital on February 3. Dr Harry Goldblatt spoke on "The Humoral Mechanism in Hypertension."

It is agreed that in hypertension there are increased cardiac output, blood volume and blood viscosity, but these do not appear to be initiating factors. The basic cause now appears to be an increased peripheral vascular resistance, which may be on a neurogenic or circulatory basis. Organic blood vessel disease is rarely widespread enough to be a cause. Vasospasm—at least when re-

ficient cause for hypertension, and is probably not neurogenic.

That a humoral mechanism is involved in hypertension is now fairly generally accepted, but the manner of its working is still debated. The finding of an initiating cause is now a major problem. Endocrine studies, particularly on the androgens, originally occupied a prominent role, but are now of questionable value. Surgery, performed on that basis, except in cases of tumors, is also of doubtful benefit. The hypophysis has been intensively studied and has even been irradiated for relief of hypertension. The value of such treatment has not been proved. Renal hypertension was formerly believed to occur only in the presence of recognizable kidney disease with impaired renal function. Innumerable attempts were made to prove a renal basis for hypertension before Dr. Goldblatt employed partial clamping of a renal artery. Even this method had been tried before, but not enough time was allowed to elapse before the results were evaluated. *Incidentally, arterial occlusion does not result in true ischemia but causes a "hemodynamic disturbance."*

In experimental hypertension in dogs, which is similar to the essential form in man, there is no impaired renal function. There is a moderate increase in heart weight, but no true *cor bovinum*. The changes in the vascular tree consist largely in increases in the media. There are none of the intimal changes of arteriosclerosis, which does not naturally occur in dogs. Decreased renal function can be brought about, however, by excessive occlusion of the renal artery, and such a decrease results in profound vascular changes. Although this happens practically overnight experimentally, the resultant condition closely simulates malignant hypertension in human beings. Vascular changes may be caused only by excessive clamping of the renal artery and the other ureter, with a decrease in kidney function. At autopsy, 98 per cent of those with renal arteriolar disease have hypertension.

The lack of a neurogenic element in this form of experimental hypertension was borne out by denervation of the kidneys and removal of the celiac and splanchnic ganglia; there was no effect on the onset of hypertension when the renal artery was clamped. This does not necessarily invalidate the clinical observations on the benefits of such forms of surgery in human beings, whose kidneys present many small "clamps," and there may be a beneficial increase of blood flow. That some substance from the kidney is involved in the phenomenon is proved by removal of the kidney, by the return of the blood pressure to normal on removal of the clamp or of the kidney to which the clamped vessel leads, by the elevation of blood pressure when the kidney is transplanted and the artery clamped, by the elevation of blood pressure when a so-called "ischemic kidney" is transplanted and perfused, and by the failure of the blood pressure to rise when the renal veins are ligated.

The presence of renin in hypertensive kidneys was postulated many years ago, but Landis was the first to establish its true pressor nature by demonstrating the lack of skin-temperature changes accompanying the hypertension. Houssay showed that blood from ischemic kidneys was more vasoconstrictor than that from normal organs, whereas Freedman et al. demonstrated the need for a substrate found in normal plasma in addition to this renal material. Houssay and Page believe that renin is an enzyme or enzymelike substance that reacts with prehypertensin, which is probably a pseudoglobulin with no pressor action, to produce hypertensin (angiotonin), which may be a polypeptide. Injection of hypertensin causes vasoconstriction and hypertension.

To investigate further the relations of the endocrines, hypophysectomy was carried out, and no effect was noted on the hypertension of the Goldblatt kidney. The removal of one adrenal gland and the medullary portion of the other also failed to inhibit the pressor action, indicating lack of control by the medulla. When both adrenal glands were removed, the blood pressure remained unchanged so long as no substitute therapy was administered, but any small amount of remaining cortex allowed hypertension to occur. The prehypertensin titer falls sharply under such circumstances, but this is prevented by the use of desoxycorticosterone acetate. This indicates that the latter substance acts directly on the plasma part of the humoral mechanism. Liver poisoning with chloroform causes a marked decrease in the prehypertensin level even when desoxycorticosterone is administered to rule out its effect on the adrenal cortex.

The treatment of hypertension depends on the cause of the particular case. That associated with unilateral renal disease may be materially benefited by *nephrectomy*. Increase of the accessory renal circulation through the spleen or other organs has shown some promise in dogs but not, so far, in man. In such dogs, only the renal artery is involved, whereas there is intrarenal disease in human hypertension. Medical treatment, except for fleeting relief from the nitrites, is unavailing. Many attempts are being made to use various tissue extracts. Hypertensinase, or angiotonin inhibitor, obtainable from many tissues but especially the kidney, has given rise to some alleged good results in animals and man. Wakelin has attempted to desensitize against renin by gradually increasing the amounts injected. But the antipressor titer is the same at the high and low levels of blood pressure. In all these attempts with tissue therapy, the question of the purity of the extract arises, for in most cases there are large amounts of both renin and inhibiting substances. The importance of the patient's temperature cannot be too strongly stressed, for those who respond invariably had some fever. Fever therapy with typhoid injections accomplished the same ends in reducing hypertension. The possibility of a nonspecific protein reaction therefore arises.

The discussion was inaugurated by Dr. Robert W. Wilkins, who reported on the crucial experiment of administering potent angiotonin to human volunteers. There was a resultant hypertension and vasoconstriction, but certain side reactions not characteristic of essential hypertension occurred. The most significant of these was an almost constant rise of venous pressure to heart-failure levels. The second contribution concerned the return of blood pressure toward or to normal on removal of a responsible diseased kidney. Therefore, hypertension is not necessarily a response to vascular disease and is not required to drive the blood through narrowed vessels, as was formerly taught. The changes, then, are not always irreversible.

Dr. Mark Altschule emphasized the presence of an increased venous pressure in most experimentally hypertensive animals as compared with diseased human beings, and therefore questioned the similarity of causation. Dr. David Ayman stated that the present surgical treatment of hypertension does not increase the renal blood flow, as demonstrated experimentally.

Dr. Lewis Dexter, in discussing the relation of the adrenal glands to this subject, stated that adrenalectomy results in a decrease of precursor in only about 50 per cent of the dogs. Evaluation of renal extracts reveals that many of them used therapeutically contain variable amounts of, or no, renin and hypertensinase. One form of therapy is to attempt the destruction of renin or hypertensin, but so

no effective material has been found. A renin inhibitor may exist but is still unknown. Hypertensinase is as yet not a definite entity, for there are many reactions from this impure, labile substance. Finally, a transfer in toto of the humoral mechanism of experimental animals to man is dangerous, for the causes of hypertension in man are variable and complicated.

In conclusion, Dr Goldblatt offered impurity of the extracts as the explanation of the elevated venous pressure observed by Wilkins. He agrees with Dr Altschule that the high-powered character of hypertensive patients is a result rather than a cause of the elevated blood pressure. However, there is a large percentage of hypertension in the sluggish Negroes of the Virgin Islands. So far as the amount of blood flow following surgery on the abdominal sympathetic ganglia concerned, he believes that clearance methods are not sufficiently accurate even in the hands of their originators. That so-called unilateral renal disease may actually be bilateral is possible on the basis that hypertension may be present even in the absence of decreased kidney function. At present there is no means of determining the hypertensive state of a kidney by the common functional tests.

## BOSTON ORTHOPEDIC CLUB

At a regular monthly meeting of the Boston Orthopedic Club held at the Boston Medical Library on February 16 Dr Charles Bradford spoke on Recent Experiences in England.

The first part of the discussion concerned the problems encountered at a base hospital about 50 miles from London where there are 1700 beds, of which 300 are for orthopedic use and 100 for convalescent patients. Injured persons arrive one to three days after an injury in the city by automobile and come in groups of 20 to 200 at one time. On admission they may be suffering from fatigue or may be in actual or incipient shock, but very few deaths result. However about 30 to 45 per cent of those injured in raids die largely from primary shock or blast, or both. Once that phase has been surmounted, the results are good, probably because of the more intelligent treatment of shock. Sixty to 75 per cent of the movable cases are orthopedic.

The primary treatment at the site of the raid is usually inadequate because of the character of the incidents and the overcrowding of the stations. Debridement, although attempted, is often hurried and incomplete and such wounds should, therefore be left open. This should not be considered analogous to compound wounds of civilian life, in which careful thorough preparation allows primary closure. Chemotherapy with the sulfonamides is invariably employed, but it is difficult to evaluate the results, for there is no correlation of amount of drug, degree and quality of debridement, amount of contamination and so forth. The tendency to place too much reliance on chemotherapy at the expense of thorough mechanical cleansing is a definite hazard. At least 50 per cent of the patients reach base hospitals infected because of inadequate debridement or faulty use of chemotherapy, or both. The proper use of the sulfonamides however probably does lengthen from six to eight to fourteen to twenty-four hours the period in which primary closure of wounds is possible.

The choice of methods of immobilization is still being debated. For a fracture of the femur there seems to be no question about the value of the Thomas splint. For fractures elsewhere, the plaster method of Orr is most popular. The splinting is more adequate than any other

method the soft tissues are protected, and a certain control of the spread of toxins is accomplished. Its foremost advantage however, is the prevention of needless tampering with the wound. Among its disadvantages is the need for ceaseless observation and intelligent care to guard against the development of pressure sores and other sequelae of edema for which no precautions are taken in application of the plaster. Little, if any, progress is being made in the treatment of shock in England as compared with that in the United States. There have been difficulties with plasma precipitation and serum is therefore being more widely used. American plasma is apparently superior and the organization for transportation and so forth in England is excellent.

In the treatment of the later stages of fractures, most of the older men favor the Orr method, for they appreciate the greater comfort to the patient as compared with the multiple dressings of the last war. The wounds look as well if not better and the clinical course is usually much improved. Amputations have been performed less frequently but chemotherapy may have had some effect on these statistics. The bacteria encountered have been largely staphylococci anaerobic and aerobic streptococci and *Clostridium welchii* but the incidence of gas gangrene has been only 0.5 per cent. This may also have decreased the number of amputations. The value of the Orr method in decreasing secondary contamination of wounds has been amply borne out by studies on the flora of wounds on surgical wards. In this way it has been demonstrated that most infections are contracted in the wards rather than being latent in the wounds. With the Orr method the opportunities for cross infections on a ward are greatly decreased.

There are the usual late complications encountered in civilian orthopedic practice but there is definitely a higher incidence of infection. Wounds on the whole are multiple. In England, plating of fractures is in great disfavor because of numerous failures which are attributable to inadequate sepsis and small plates and screws that pierce only one cortex. But in an attempt to rehabilitate quickly, especially in the air corps, this conservatism has given way to radicalism in the form of an extravagant use of bone grafts (Watson Jones). It is often impossible to plate or graft a fracture, and here the Roger Anderson or some similar apparatus has a large scope. In 65 cases in which this splint was employed there were no failures, and there was a wide applicability. There is need of much technical study, skill and constant care to prevent failures however. One excellent feature is the opportunity for making patients ambulatory in a short time, and for transporting fractured femurs and patients with multiple fractures. When there are widespread wounded men in remote places a trained surgeon and an assistant can obtain immobilization with this apparatus without the necessity for x-ray examinations and the patients may then be transported to base hospitals in safety and comfort.

The problems in a bombed city itself are numerous. To relieve the hospitals of the large number of cases, it is necessary to have well trained first aid parties, preferably under the direction of a local physician. Such groups decide whether the slightly injured may return home or should be sent to first aid centers, which are not in hospitals but are easily accessible and are under the jurisdiction of competent doctors and nurses. The practical application of first aid technique is taught is often faulty and such things as sepsis naturally are useless in the streets during a blackout. The amount of first-aid treatment at the spot has been found to impede hospital administration.

tion and is accordingly confined to the control of major hemorrhage and the splinting of obvious fractures, with especial care of suspected spinal injuries.

When one attempts to treat severely wounded persons in the midst of a "blitzed" city, the available hospitals are merely used to best advantage. They are protected physically by sandbags, fire watchers and so forth, but some damage still occurs. Casualty rooms should be on the ground or preferably a basement level. Co-ordination must be of two kinds: interhospital and intrahospital. When most of the damage occurs in one part of a city, it is imperative not to overload the physical and personnel facilities of the neighboring institutions. For this purpose of interhospital co-ordination, a center is advisable, but this is so far not being well carried out in England. In a given hospital, the number of admissions is entirely unpredictable, and the staff must respond immediately and improvise whenever necessary. Three important groups should be organized: that for admission, in which competent clinical judgment is necessary; that for the treatment of shock, which can function in any large space equipped with many beds, blankets and intravenous fluids; and surgical operating teams, which should have two or three tables in one room rather than a similar number of rooms. The proper choice and administration of anesthesia cannot be too strongly emphasized. A good supervisor can control a large group if the cases are well arranged. Nitrous oxide is probably greatly underrated, and Pentothal sodium has been found excellent, especially in shock. At Pearl Harbor, a large amount of drop ether was administered, and this method is strongly advocated as being easiest, if not safest, especially in the hands of untrained anesthetists.

In conclusion, the role of the fire and public utilities departments as a first line of defense was emphasized.

**Dr. Ernest P. Boas, M.D.**

## BOOK REVIEWS

*Treatment of the Patient Past Fifty.* By Ernst P. Boas, M.D. 8°, cloth, 324 pp., with 19 illustrations. Chicago: The Year Book Publishers, Inc., 1941. \$4.00.

Pediatrics and public-health education, by extending the average duration of life, have made geriatrics a very important department of medicine, and Dr. Boas has drawn on his wide practical experience and extensive study in this field to write a book notable for thoroughness and clarity. He defines senescence by indicating the factors that, singly or in combination, produce the condition, and the section devoted to cardiovascular diseases, which constitutes more than one third of the book, should be of great value to the general practitioner, who is usually the first to encounter the symptoms of physical or psychologic degeneration. Although fifty is taken as a dividing line, one must avoid being arbitrary in this matter, since there are persons in whom warning signals are evident earlier, and many others with healthy bodies and happy minds who are free from such symptoms until a much later period.

The author has given excellent advice on the aftercare of patients with coronary-artery involvement, as well as a pertinent explanation of the relation between these diseases and diabetes mellitus, with a wise warning against the use of insulin in such cases.

Of equal significance is the chapter on diseases of the lungs, which stresses the effect of such conditions on the heart and circulation. It is surprising, however, that more attention has not been directed to some of the blood diseases occurring in the middle years.

Since medical or surgical treatment has less of permanent success in the elderly, serenity and comfort become prime objectives; and when, as sometimes happens, old age is more a state of mind than of physical degeneration, the treatment is correspondingly advantageous; however, in the majority of conditions, Dr. Boas might well have indicated more fully the definite treatment in these situations.

The book offers nothing that is new to specialists in various fields, and is primarily a general textbook of medicine, with emphasis on diseases occurring due to senescence.

*Infant Nutrition: A textbook of infant feeding for students and practitioners of medicine.* By William McK. Marriott, M.D. Revised by P. C. Jeans, M.D. Third edition, cloth, 475 pp., with 31 illustrations. St. Louis: The C. Mosby Company, 1941. \$5.50.

Dr. Marriott's book first came out eleven or twelve years ago with the avowed purpose of presenting the infant nutrition on a relatively simple, yet scientific, basis. It did that, or helped to do it. No pediatricians used Marriott's method for the various ways of feeding babies, — as doubtless there always will be, — any of which may be successful so long as it is adherence to certain underlying principles were emphasized, and still is. Dr. Jeans has not altered the general structure of the volume, but merely brought in factors that keep the subject thoroughly up to date.

To the specialist in pediatrics, all this ought to be familiar ground of course, but to the general practitioner, to the student in medical school, it will be a most useful text. The viewpoint is neither too narrow nor too broad, and the book is well recommended.

*Health Resorts of the U. S. S. R.: A symposium of articles.* Compiled from data of the Central Institute of Balneology in Moscow. Editor: Dr. I. A. Pertsov. 8°, cloth, 270 pp., with 45 illustrations. Moscow, Russia: The U. S. S. R. Society of Cultural Relations with Foreign Countries (V. O. K. S.).

This is a comprehensive work on the health resorts of Russia, which abounds in innumerable mineral springs, deposits of medicinal muds. At present, many of these places in the Soviet Union possess natural curative agencies covering all known types of caliche mineral waters. The vast territory of the nation has diverse climates: humid, subtropical, arid, subarid and mountainous. Stalin Five-Year Plan included the reconstruction of existing health resorts and the building of new retreats for the benefit of the people.

*The Premature Infant: Its medical and nursing care.* Julius H. Hess, M.D., and Evelyn C. Lundeen, R.N. cloth, 309 pp., with 74 illustrations. Philadelphia: J. Lippincott Company, 1941. \$3.50.

This is by far the most complete and satisfactory treatment on the premature infant that has ever come to the attention of the reviewer, and every physician and every nurse charged with the care of such infants would do well to have the volume at hand. It is specific down to the minutiae of procedure, and scarcely a question that arises in this field is not anticipated. A mere glance at the well-chosen illustrations often shows exactly how that should be done.

